the epidemiology of infections with Clostridioides difficile and multidrug-resistant bacteria, and faecal microbiota transplantation as an intervention strategy

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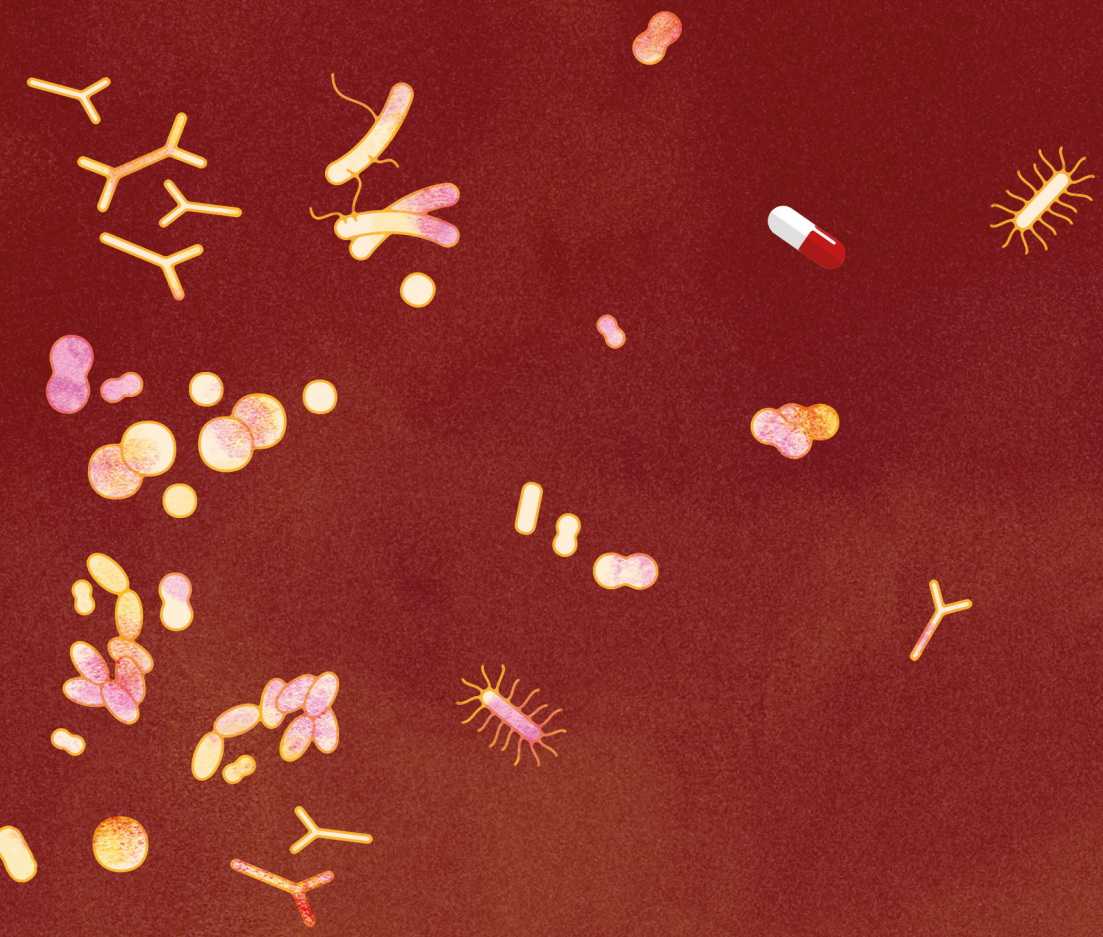
Chapter 11

Recommendations for the future



Recommendations for future policies and for studies and surveillance on the epidemiology of infections with *C. difficile* and multidrug-resistant bacteria

Periodic studies and/or surveillance are needed to monitor the changes in incidence and spread of *C. difficile* and MDRO. MDRO surveillance is performed by the RIVM for MRSA, carbapenemase-producing Enterobacterales and *Pseudomonas aeruginosa*, and for carbapenem-resistant *Acinetobacter baumanii-calcoaceticus complex*. Annual reports summarise the findings and provide recommendations. The data on colistin resistance that are described in **chapter 4** were collected during participation in a study coordinated by the European Centre for Disease prevention and Control. In the future, we advise to initiate surveillance of colistin resistance via the Dutch Infectious Disease Surveillance Information System-Antibiotic Resistance (ISIS-AR).[1] This means that results of colistin resistance tests, that are performed in the daily routine of Dutch laboratories are uploaded into a web-based database. In this way, increasing trends in the incidence of colistin resistance can be detected timely. In case of a clear increase, observed via ISIS-AR, we advise to initiate national sentinel surveillance with further genetic characterisation of the colistin resistance. Monitoring colistin resistance in the Netherlands is important because:

- The results from the study described in **chapter 4** show that colistin-resistant isolates are present in the Netherlands.
- Colistin is a last resort antibiotic.
- Colistin resistance is increasing worldwide[2,3] and could be introduced by travel or patient transfers from other countries.
- The use of colistin in SDD/SOD should be re-evaluated in case of an increase in colistin resistance as we found a clear association between detection of colistin resistant Enterobacterales and previous use of colistin in SDD/SOD in **chapter 4.**
- Colistin resistance of *Klebsiella pneumoniae* is of special interest, since hypervirulent forms have been found in a pilot surveillance in the Netherlands, carbapenemase-production has been recognised in hypervirulent strains in Europe[4] and colistin-resistant carbapenem-resistant strains have also already been described.[5,6]

The surveillance of routine diagnostic testing results should be combined with stimulating all medical microbiological laboratories to test all Enterobacterales isolates for colistin resistance with methods that are more reliable than automated testing methods and to test for all known *mcr* genes. At the RIVM, colistin resistance testing should be included in the national CPE surveillance since isolates that are both carbapenem-resistant and colistin-resistant are the most threatening isolates. Testing at the RIVM should include at

least testing for *mcr* genes, but it preferably also includes testing for colistin resistance by BMD and detection of chromosomal mutations leading to colistin resistance.

The colistin resistance rate described in **chapter 4** is likely an underestimation. A study in which all invasive *E. coli* and *K. pneumoniae* isolates (including the carbapenem-non-susceptible) are screened for colistin resistance by BMD during a short period would provide insight in the burden of colistin resistance in the Netherlands. These surveys should be repeated every few years to assess trends in colistin resistance.

Most previous studies investigating colistin resistance have only examined *mcr* genes and/or specific patient categories, such as travellers or ICU patients. It is also interesting to examine the prevalence of intestinal colonisation with colistin-resistant bacteria among the general population in the Netherlands. This has been investigated for ESBL- and carbapenemase-producing bacteria in the PIENTER study,[7-9] but not yet for colistin-resistant bacteria. From a One Health perspective, exploring colistin resistance in animals and wastewater is also useful.

The Dutch MRSA surveillance should focus more on monitoring community-onset MRSA infections. For example, monitoring of MRSA MLVA-type MT4627 is important, as this strain has the potential to spread rapidly and cause severe disease. Since June 2018, more than 110 cases with MRSA MT4627 have been found. At least one case had severe staphylococcal scalded skin syndrome. Presumably, this number of cases is an underestimation, since general practitioners frequently do not send patients samples for microbiological diagnostics in case of no response to first-line antibiotic treatment. In the previous years, spread of several MRSA MLVA types in the community have been detected, some in special patient groups or on special locations. The microbiological information should be communicated to the municipal health services, medical microbiological laboratories and general practitioners more rapidly to develop and implement interventions as soon as possible. General practitioners can be informed more on the problem of community-acquired MRSA and they should be encouraged to send in samples for culture. This can be achieved by adapting guidelines for general practitioners and by publications in journals focussing on general practitioners. Furthermore, municipal health services can aid in the assessment of the problem extent. New and interesting is the contribution of pharmacists by providing information on antibiotic prescription data. In this way, more insights into the extent of an outbreak may be obtained than via microbiological laboratories and municipal health services.

As is the case for MRSA testing, general practitioners should also be informed on the importance of CDI testing in patients with diarrhoea and certain risk factors for CDI. Patients with community-onset CDI are underreported because general practitioners frequently do not request CDI tests in these patients.[10] CDI surveillance among community patients with diarrhoea would also be useful. This may enable investigations on the incidence and spread of CDI in the community and on the reason for the increase

of community-onset CDI among hospital patients found in the national sentinel CDI surveillance. Every medical microbiological laboratory should test all diarrhoeal samples send in by general practitioners for *C. difficile* with a molecular test with confirmation by a toxin enzyme immune assay to demonstrate the presence of free faeces toxin. This advice should also be incorporated in guidelines for general practitioners.

Since 2021, the Dutch *C. difficile* reference laboratory is replaced by a *C. difficile* expertise centre, with five laboratories participating in the sentinel surveillance instead of the previous 22. In 2023, the laboratory implemented core-genome multilocus sequence typing (cgMLST) as replacement for PCR ribotyping; cgMLST provides more discriminatory power, better reproducibility and is easier to standardise than PCR ribotyping when properly chosen allelic thresholds are applied.[11] In this way, local and national trends of CDI can still be monitored and the expertise is maintained.

Recommendations for the future of FMT

The field of FMT is evolving rapidly. The number of studies on FMT has increased tremendously in the past decade. Although the knowledge on working mechanisms, safety and new indications of FMT is increasing, there is still much left to be studied.

Until further evidence becomes available, other indications for FMT than recurrent CDI should be limited to the research setting or, in the absence of alternative therapeutic options, in a compassionate use setting. RCTs with large sample sizes, adequate controls (preferably making blinded randomised designs possible, e.g. by using an autologous faecal suspension) and intensive and standardised follow-up are crucial for the decision to register FMT for more indications than rCDI. Rational faeces donor selection may improve efficacy of FMT,[12] which necessitates knowledge on the pathophysiology of the disease and the relevant characteristics of the microbiome, but also availability of several different donors. Especially for ulcerative colitis, rational donor selection appears to be important.[13] Future studies should also answer the question whether gut microbiota baseline profiles or patient characteristics can predict who will benefit from FMT. Herein, the use of appropriate methods for the (preparation of) microbiota analysis and assessment of possible confounding factors are crucial. For the assessment of the gut microbiota composition, standardised methods should be used to minimise inconsistency in results. Concomitantly, functional analyses of the gut microbiome will have a crucial role in determining which taxa are important in each disease. It is also important that more evidence becomes available on the required number of FMTs and the necessity of pre-treatment with antibiotics and bowel lavage for each disease.

Following the report on transmission of MDRO by FMT,[14] the importance of standardised donor screening became evident. International guidelines on donor screening have been

contemplated by several FMT experts.[15] It is important that stool banks have similar strict screening protocols with sensitive and reliable pathogen detection methods and that they are evaluated by independent organisations to ascertain that they follow the international guidelines. However, screening protocols could differ to some extent between different countries or regions depending on the local epidemiology of infectious diseases. Despite these guidelines, there are still several uncertainties regarding donor screening. The risks of UTIs due to antibiotic susceptible uropathogenic *E. coli* transmitted by FMT and also the relation of other types of infections with FMT should be further examined by independent experts. It may be worthwhile to include gut microbiota analysis with investigation of the abundance of certain genera or species or procarcinogenic bacteria in the donor screening protocols.[16] Furthermore, it is important to monitor (S)AEs properly and in a standardised manner and to report them to independent assessors with expertise in this field. It is also important to examine potential long-term SAEs, preferably via national or international registries.[17] Predisposing or deteriorating factors for the diseases of the patient, if known, should be examined in the donor to prevent potential worsening of symptoms. When the risk of adverse events of FMT is increased due to patient-specific factors, storage of an autologous faecal suspension may be considered.

The safety of FMT could be improved, but safety issues with FMT will remain, as the optimal composition of a faecal suspension cannot be assessed with certainty due to limitations of testing methods and it varies over time and per faecal suspension for each donor. Providing identical faecal suspensions for different patients is not possible. A potential solution to this is the use of live biotherapeutic products.[18] Hopefully, FMT will be replaced by standardised live biotherapeutic products (LBPs) in the future. This will improve the safety, but also the burden for patients. Studies on the LBPs RBX2660[19] and SER-109[20] are at an advanced stage and have shown promising results. RBX2660 has recently been approved by the FDA for the treatment of recurrent CDI. However, it has inferior cure rates compared to that of FMT. Until a LBP with cure rates similar or superior to that of FMT has been approved, FMT will remain the best treatment option for patients with multiple recurrent CDI.

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