

Case Discussion

Ethical Questions Concerning the Use of Molecular Typing Techniques in the Control of Infectious Diseases

Babette O. Rump*, Municipal Health Service GGD Midden-Nederland
Frits Woonink, Municipal Health Service GGD Midden-Nederland

*Corresponding author: Babette O. Rump, Postbus 51, 3700 AB Zeist, The Netherlands. Tel.: +0031 (0)30 6086086; Email: brump@ggdmn.nl

This case for discussion highlights some of the ethical difficulties that may arise in the use of molecular typing techniques in the control of infectious diseases. Molecular typing techniques offer evidence (stronger than regular epidemiological exploration of sources and contacts) for claims about infection routes. Such evidence will mean that public health authorities need to think about how to respond ethically to causal responsibility for contagion. In this context, questions are raised about the use of molecular typing methods for source and contact tracing in the control of infectious diseases.

Case for Discussion

Contact tracing and source identification are important tools in the control of infectious diseases. A combined approach of an epidemiological and microbiological investigation is the gold standard in outbreak management. The microbiological investigation has long been based on the cultivation of microbes, showing no more than the causative agent, but over the past decades new genetic techniques based on molecular typing methods have been introduced. Molecular typing techniques reveal the genetic fingerprint of a microbe (Patel and Graham, 2007) and this may offer valuable insights into transmission patterns. Several different typing techniques are available based on different principles, some addressing the whole genome others addressing specific sequences within the genome, but all are suitable for identifying microbiological strain relatedness. In the control of infectious diseases, knowledge about strain relatedness in a host population, for instance, can discriminate outbreaks from pseudo-outbreaks, reveal more precise information on transmission patterns and identify the source of infection. Further comparison of the particular micro-organism with widely available genomic libraries allows conclusions to be drawn on the evolution and timing of the introduction of the microbe

into the host population (Belkum Van, 2002; Patel and Graham, 2007; Kretzschmar *et al.*, 2010). In these ways, microbial techniques complement epidemiological investigation, offering better understanding of an outbreak, and thereby ensuring that interventions are targeted at only those contacts really at risk.

However, the use of molecular typing techniques in outbreak management also has limitations. A genetic fingerprint related to molecular typing does not have the uniqueness of a fingerprint known from forensic medicine. The technique needs to be used and understood within the context of the epidemiological investigations. Molecular typing techniques will, however, give more precise information on the relational patterns between different microbes found in an outbreak and this will inevitably reveal contacts that have occurred between the individuals hosting them. This raises a number of ethical issues and we present two different examples to provide a context to discuss them.

The first example relates to a recent response to a hepatitis A outbreak by our MHS (Municipal Health Service) (Rump *et al.*, 2012). Here, the use of sequencing confronted us with an unexpected dilemma. Hepatitis A is a faecal–oral transmittable virus that is no longer endemic in the western world and can therefore easily cause significant outbreaks if introduced into this

disease-naïve population (Pham *et al.*, 2005). Outbreaks of hepatitis A in European countries are usually controlled by offering post-exposure immunization (Payne and Coulombier, 2009). This outbreak came to our attention with the notification of seven Hepatitis A infections within one family of Dutch-Moroccan descent. The virus was subsequently introduced to two day-care centres and resulted in a large and costly vaccination campaign. Several members of the index family had visited Morocco in the previous months and none had consulted a travel clinic for pre-travel vaccination advice. Two viral strains from the family were genotyped and matched with a sequence that was similar to sequences found among infected travellers returning from Morocco, suggesting that the family had contracted the virus during their stay in Morocco and introduced the virus into the day-care population back in the Netherlands. An administrator of the health department in the municipality raised the question whether the family could be held responsible for the costs and expenses resulting from the management of this outbreak. What is the ethical way to respond to such issues? Should such information be shared? Who with? How should we think of responsibility in this kind of case? Is it appropriate to think of billing those 'responsible' for such harm, where they have failed to follow travel advice? How, if at all, is the potential impact on public attitudes to 'foreigners' relevant to thinking about this case?

The second example concerns an invasive Group A-Streptococcal (GAS) infection that caused the death of a grandmother. A GAS bacterium infection usually causes either no symptoms or only mild symptoms, such as impetigo or a throat infection. Occasionally, however, the GAS bacterium can cause an invasive infection with severe illness and even death. An invasive GAS infection is associated with specific host factors such as underlying illnesses on the one hand and intensive contact with a person diagnosed with an invasive GAS infection on the other. For this reason, household contacts of an index case are considered to be at increased risk of serious disease or mortality due to GAS (Prevention of Invasive Group A Streptococcal Infections Workshop Participants, 2002). Our MHS therefore conducts a contact investigation and follow-up after each notification. Household contacts are offered chemoprophylaxis and advised to maintain a heightened index of suspicion for subsequent GAS disease for 30 days after exposure.

Routine contact tracing in this case revealed that the grandmother had been watching over her grandchildren

in the days before her death and both children reported having had a throat infection whilst cared for by their grandmother. Our MHS screened the children for GAS carriage and found them both to be hosting a GAS strain genetically identical to the one isolated from the grandmother after her death. This knowledge justified the heightened index of suspicion and the use of chemoprophylaxis in these children, but it also suggested that the children were the source of the infection that caused the death of their grandmother. Should this additional information be shared with the family? Should it be shared with the public and the media? Does the family have any right to control the information? How important is transparency in such cases? Does it outweigh the potential harm to the family from disclosure?

The use of molecular typing techniques in infectious disease control brings to mind a number of ethical questions. The technique offers evidence (stronger than regular epidemiological exploration of sources and contacts) for claims about infection routes, and hence claims about causal responsibility for contagion. Such claims may also provoke controversial thoughts about moral responsibility. However, if public health interventions may result in judgments about moral responsibility for infection, citizens may in the future become less willing to cooperate in contact tracing and other investigations. Questions also arise about consent for such tests. Should we require that a host must give permission for the analyses of microbes in their blood or tissue samples, or are arguments for population benefits or the common good strong enough to justify investigations without consent? More generally, under what conditions are we justified in using this technology for source and contact tracing in the context of the control of infectious diseases?

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Conflict of Interest

None declared.

References

- Belkum Van, A. (2002). Molecular Typing of Micro-Organisms: At the Centre of Diagnostics, Genomics and Pathogenesis of Infectious Diseases? *Journal of Medical Microbiology*, **51**, 7–10.
- Kretzschmar, M., Gomes, M. G., Coutinho, R. A. and Koopman, J. S. (2010). Unlocking pathogen genotyping information for public health by mathematical modeling. *Trends in Microbiology*, **18**, 406–412.
- Patel, S. J. and Graham, P. L. (2007). Use of Molecular Typing in Infection Control. *The Pediatric Infectious Disease Journal*, **26**, 527–529.
- Payne, L. and Coulombier, D. (2009). Hepatitis A in the European Union: Responding to Challenges Related to New Epidemiological Patterns. *Euro Surveillance*, **14**, Available online: <http://www.eurosurveillance.org/viewarticle.aspx?articleid=19101>.
- Pham, B., Duval, B., De Serres, G., Gilca, V., Tricco, A. C., Ochnio, J. and Scheifele, D. W. (2005). Seroprevalence of Hepatitis A Infection in a Low Endemicity Country: A Systematic Review. *BMC Infectious Diseases*, **5**, 56.
- Prevention of Invasive Group A Streptococcal Infections Workshop Participants. (2002). Invasive Group A Streptococcal Disease Among Household Contacts of Case Patients and Among Postpartum and Postsurgical Patients: Recommendations from the Centers for Disease Control and Prevention. *Clinical Infectious Diseases*, **35**, 950–959.
- Rump, B. O., Visser, O., te Wierik, M. J. M., Vennema, H. and Fanoy, E. B. (2012). Use of PCR for detection of faecal HAV as a screening tool in an outbreak of hepatitis A in daycare centres. *Epidemiology and Infection*, doi: 10.1017/S0950268812000854.

Molecular Typing: Use with Care

Ewout Fanoy*, National Institute for Public Health and the Environment, the Netherlands

Albert De Neeling, National Institute for Public Health and the Environment, the Netherlands

*Corresponding author: Ewout Fanoy. Email: Ewout.Fanoy@rivm.nl

Reaction on Questions Raised by Rump and Woonink

Rump and Woonink describe two interesting cases illustrating ethical dilemmas that can emerge after genetic typing during outbreak investigations (Rump and Woonink, 2012). One of their cases involved the typing of a group A streptococcal strain that caused the death of a woman and infected her grandchildren. Typing showed the strains of the woman and the children to be similar. However, strict identity of bacterial strains cannot be assessed. ‘All strains are equal, but some are more equal than others.’ Otherwise stated, when microorganisms are indistinguishable from each other based on genetic typing, they can still be unrelated. The discriminative power differs per typing method and depends on the length and natural variability of the DNA sequence used for comparison. A strain

comparison based on full genomic sequence typing provides an optimal discriminative power, but this technique is still laborious and therefore not used in patient care and outbreak control yet.

A dilemma in both cases is the issue of ‘blame’. Who is the source of the outbreak? Who infected whom? Such questions can be financially, legally or emotionally driven. Patients may ask health professionals to give information about genetic sequences of potential sources. For example, in 2007, recently HIV-infected Dutch men having sex with men filed a criminal case against three other men, accusing them of deliberately subcutaneous injecting them with HIV-positive blood (van der Kuyl *et al.*, 2011). The genetic sequence analysis of the HIV strains of both the defendants and the accused were used as evidence. Non-medical use of genetic information could make patients or contacts of patients more reluctant to cooperate during outbreaks in the future.