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Household transmission and disease transmissibility of a large HAV outbreak in Lazio, Italy, 2016–2017

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ABSTRACT

A major outbreak of Hepatitis A Virus (HAV) has swept through Europe between mid-2016 and 2017, mainly within the community of men who have sex with men (MSM). Over the same period, about 1000 outbreak-related cases of acute Hepatitis A (AHA) were recorded in Lazio region, Italy.

We calibrated a Bayesian model to reconstruct likely transmission events within all 44 households where multiple infections were recorded, representing a total of 103 cases from the HAV outbreak in Lazio. Based on information on the observed times of symptom onset, we estimated the probability distribution function of the HAV generation time and used it to compute the effective and instantaneous reproduction numbers for the considered outbreak from the overall epidemic curve (N = 998 cases).

We estimated a mean generation time of 30.2 days (95%CI: 25.2–33.0) and an effective reproduction number of about 1.63 (95% CI: 1.35–1.94). Transmissibility peaked in January 2017, shortly before targeted awareness and vaccination campaigns were put in place by health authorities; however, transmission remained above the epidemic threshold until June 2017. Within households, children (0–15) and young adults (16–30) infected preferentially individuals of the same age class, whereas transmission within older age groups was substantially homogeneous.

These results suggest that the implemented interventions were able to slow down HAV transmission, but not to bring it rapidly to a halt. According to our estimates of the HAV transmissibility, about 50% of the at-risk persons should be immunized to prevent similar outbreaks in the future. Our results also indicate spillover from community transmission to household members, suggesting the opportunity of vaccinating household contacts of cases to prevent further spread of the epidemics.

1. Introduction

Acute Hepatitis A (AHA) is a viral self-limiting disease that normally resolves spontaneously. Hepatitis A virus (HAV) is transmitted predominantly via the fecal-oral route, through contaminated water and food or by person-to-person contacts (Lanini et al., 2018). In low-income countries, HAV circulation is mainly maintained by poor socio-economic conditions including high housing density, poor hygiene and water sanitation systems. In high-income countries, where incidence is low, HAV may be transmitted by different modes, including same-sex intercourse between males and needles/paraphernalia sharing among people who inject drugs (PWID) (Lanini et al., 2018). The overall reduction in HAV seroprevalence due to the decreasing incidence in recent decades is creating large reservoirs of susceptible individuals, especially among younger age groups (European Centre for Disease Prevention and Control (ECDC), 2016). As a consequence, several outbreaks of AHA have been described in high-income countries in recent years, especially in US and Europe, related to new risks associated with globalization and people movements (Lanini et al., 2018).

Since the summer of 2016, a large HAV outbreak has been spreading throughout Europe, predominantly affecting the community of men-who-have-sex-with-men (MSM) (European Centre for Disease Prevention and Control, 2018). During 2017 only, the European Center for Disease Control reported over 20,000 laboratory-confirmed cases from 26 countries (a four-fold incidence compared to previous years) with male-to-female ratio topping at 4.8 at the peak of the outbreak in

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March (European Centre for Disease Prevention and Control, 2018). During the summer of 2017, the male-to-female ratio has decreased rapidly while case counts remained comparably high, indicating an increasing frequency of spillover events through other types of contacts, such as household transmission (European Centre for Disease Prevention and Control, 2018). A local outbreak due to the same HAV variant that was circulating in Europe has occurred in Lazio region, Italy, between August 2016 and the end of 2017, mainly involving the metropolitan area of Rome (Lanini et al., 2017). The outbreak consisted of 1013 HAV cases and predominantly affected young MSM, with an average male-to-female ratio of 8.3 (Lanini et al., 2017). In an effort to limit the spread of the outbreak, a prevention campaign has been conducted in Lazio since February 2017, aimed at the adult population aged between 18 and 45 years and especially targeting MSM. This intervention has allowed not only the dissemination of information about the mode of transmission and prevention but also promoted the vaccination of a population at risk.

In order to quantify many aspects of the transmission dynamics of an outbreak, it can be useful to have a characterization of the infection's generation time, defined as the time elapsed from the acquisition of the virus by an infector and its secondary case (Nishiura, 2010). In particular, the statistical distribution of the generation times shapes the temporal evolution of the epidemic curve, and the knowledge of such distribution allows for a robust estimate of the reproduction number (Wallinga and Lipsitch, 2007), i.e. the average number of secondary infections caused by an infectious individual. The reproduction number is an important indicator of the transmissibility of the infection during an outbreak: when its value is above 1, the disease can spread in the population with intensity proportional to the reproduction number; when it goes below 1, for example as a consequence of infection control activities or depletion of susceptible population, the outbreak is destined to fade out.

An easily measured proxy for the generation time is the serial interval, i.e. the time elapsed between the symptom onset of two linked cases (Fine, 2003). This measure is an accurate representation of the generation time if the incubation period (i.e. the time between infection and symptom onsets) varies little across different individuals. For HAV, currently available estimates of the serial interval (Simpson, 1948; Brodribb, 1952) are based on historical data with small sample size (Simpson, 1948; Vink et al., 2014) and are reported as average values. Furthermore, the incubation period for HAV is highly variable, ranging from 15 to 50 days, making the serial interval a potentially biased estimate of the generation time.

2. Methods

Here, we used data from HAV cases in Lazio to provide novel estimates on the generation time and to estimate the outbreak reproduction numbers. The outbreak consisted of 1013 AHA cases. Of these, 15 were caused by different HAV variants, as shown by molecular analyses (Lanini et al., 2017), and were excluded from the computation. Using information from the remaining 998 cases, we reconstructed likely transmission links in the subset of cases occurring in households with multiple infections (103 cases in 44 households) and estimated the probability distribution of the generation time (i.e., the time elapsed between two linked infections). Subsequently, we applied the renewal equation (Wallinga and Lipsitch, 2007) to data from the overall outbreak to compute the instantaneous reproduction number, using the previously obtained estimate for the distribution of the generation time. Estimates of the generation time distribution were also used to estimate the effective reproduction number.

2.1. Reconstruction of transmission links in households

We adapted a previously developed model for the reconstruction of transmission links from the spatio-temporal relatedness of observed dengue cases (Guzzetta et al., 2018) to accommodate the temporal sequence of HAV cases occurring within the same household. In particular, we assumed that, at any time t, a susceptible individual j within a household is exposed to a force of infection

$$\lambda_j(t) = \sum_{z \in Z_j(t)} \alpha \Gamma(t - E_z; a, b) + \sum_{i \in H_j(t)} \beta \Gamma(t - E_i; a, b)$$

where $Z_j(t)$ is the subset of the 998 cases which were infected before time t and were outside the household of j, α is a scaling factor accounting for the probability of acquiring infection from outside the household, $H_j(t)$ is the set of individuals infected before time t in the household of j, β scales the disease transmission rate within households, E_x is the time of infection of individual x and $\Gamma(\tau; a, b)$ is the probability distribution function of the generation time τ, which is assumed to be a gamma function with shape parameter a and rate parameter b. The generation time can be interpreted as the average profile of infectiousness of each individual over time.

We estimated the unknown parameters $\theta = \{\alpha, \beta, a, b\}$ and the source of infection for all cases using a Monte Carlo Markov Chain (MCMC) procedure. At each step, all parameters in θ are updated using reversible normal jumps. For each case j, the source of infection k_j was chosen from $H + 1$ candidates: either one of the H household members infected before j, or a generic source outside the household, i.e. not associated to a specific individual infector. k_j was selected among all candidates by a multinomial sample with probabilities proportional to each candidate's contribution to the force of infection on day E_j, i.e. $\beta\Gamma(E_j - E_i; a, b)$ for the H household members, and $\sum_{z \in Z_j(E_j)} \alpha\Gamma(E_j - E_z; a, b)$ for acquisition of infection outside the household (Guzzetta et al., 2018). Note that the probability of k_j being the infector of j was not conditioned on the probability that k_j was the infector of other cases in the dataset.

The likelihood of the parameter set and of the sampled sources of infection is given by:

$$L(\theta) = \prod_j P(j, k_j)\, Q(E_j)$$

where

$$P(j, k_j) = \begin{cases} \sum_{z \in Z_j(E_j)} \alpha\Gamma(E_j - E_z; a, b) \text{ if } j \text{ acquired infection outside the household} \\ \beta\Gamma(E_j - E_{k_j}; a, b) \text{ if } j \text{ acquired infection from household member } k_j \end{cases}$$

and $Q(E_j)$ is the likelihood that j has not been infected before E_j, namely $Q(E_j) = \exp(-\int_0^{E_j} \lambda_j(t)dt)$.

The parameter set and the sources of infection were accepted on the basis of the likelihood values according to a Metropolis-Hastings algorithm. Uninformative (uniform) priors were assumed for all parameters.

In our dataset, the times of symptom onset of all considered cases are known, but not the times of infection E. Therefore, the time of infection for each case was imputed by subtracting from the time of symptom onset an incubation period sampled from a normal distribution with a mean of 28 days and a standard deviation of 4.67 days (European Centre for Disease Prevention and Control (ECDC), 2016; Dotzauer and Kraemer, 2012). The MCMC procedure was repeated 2000 times, after re-sampling the set of infection times E. The 2000 MCMCs were run for 100,000 iterations each, and the last 500 iterations of each run were pooled together. This resampling procedure was demonstrated to provide a robust estimation of parameter variability (Guzzetta et al., 2018).

2.2. Reproduction numbers

The probability distribution function of the generation time

estimated from the reconstruction of transmission links within households was used to determine the effective reproduction number of the outbreak, via the exponential growth rate r of the epidemic curve (Nishiura, 2010; Manica et al., 2017):

$$R_e = \frac{1}{\int_0^\infty e^{-rt}\,\Gamma(t,\ a,\ b)dt}$$

We computed 10,000 estimates of R_e by sampling a and b from the joint posterior distribution and the exponential growth rate r from a normal distribution, whose average and standard deviation were obtained from fitting the time series of cases in the phase of exponential growth (weeks 40–55 since January 1st, 2016). As a sensitivity analysis, we evaluated the robustness of the estimated R_e with different choices on the phase of exponential growth by considering all combinations of time windows starting between week 37 and 40 and ending between week 55 and 58.

We also estimated the instantaneous reproduction number R_t using the renewal equation (Nishiura, 2010; Manica et al., 2017):

$$C(t) = \mathrm{Pois}\left(R_t \sum_{s=1}^{t} C(t-s)\Gamma(s;\bar{a},\ \bar{b})\right)$$

where $C(t)$ is the total number of cases with symptom onset at time t, Pois(λ) is a Poisson sampling with rate λ, and $\bar{a}$ and $\bar{b}$ are the means of the posterior distributions of a and b. The likelihood is therefore:

$$L = \prod_{t\geq 1} p\left(C(t),\ R_t \sum_{s=1}^{t} C(t-s)\Gamma(s;\bar{a},\ \bar{b})\right)$$

where $p(k,\lambda)$ is the probability mass function of a Poisson distribution (i.e. the probability of observing k events if these events occur with a known rate λ). We estimated mean and 95% credible intervals of R_t by MCMC.

3. Results

Between 2016 and 2017, 1013 cases of AHA occurred in Lazio region; one hundred and three cases belonged to 44 households (Table 1). This analysis identified 33 individuals with transmission from household members (18 systematically, and 15 in at least 75% of the reconstructed transmission chains), 45 cases were classified as acquiring HAV infection outside the household, likely through contacts with infected persons in the general community. The source of infection for the remaining 25 cases was not robustly identified (Fig. 1).

According to the reconstructed transmission links, the majority of adult males were infected outside the household, while at least half of children and women were infected by household members (Fig. 2). In addition, adult males constituted a larger share of infectors (71% of the total) than of infected household members (52%). Transmission events were highly assortative by age for children and younger adults (Fig. 3), and more homogeneously distributed across age groups when the infector was above 30 years of age.

The estimated average generation time for HAV was 30.2 days (95%CI: 25.2–33.0; parameters of the gamma distribution: shape ± standard error: 2.80 ± 0.251; scale ± standard error: 10.9 ± 1.59), which is in line with previous estimates of the serial interval (between 26.9 (Brodribb, 1952) and 28 days (Simpson, 1948)). The average probability distribution function for the generation time had a 95%CI of 6–75 days. Indeed, all cases with serial interval higher than 75 days were systematically classified by the transmission link reconstruction model as acquired outside the household, Fig. 1. In addition, the model-reconstructed transmission events included a number of cases in which the infector developed symptoms after the infected household member (i.e., with a negative serial interval), due to the highly variable incubation times of HAV and to the more rapid development of infectiousness (about two weeks before symptom appearance (Dotzauer and Kraemer, 2012; European Centre for Disease Prevention and Control (ECDC), 2016)).

We estimated an exponential growth rate of $r = 0.124 \pm 0.018$ weeks^{-1} for the epidemic curve during weeks 40 to 55 (Fig. 4a); combined with the above estimates for the probability distribution function of the generation time, we obtained a reproduction number of $R_e = 1.63$ (95%CI: 1.35–1.94). The estimate of R_e obtained with different choices for the exponential growth phase was very stable, ranging from 1.58 to 1.64. The instantaneous reproduction number R_t, estimated by the renewal equation, shows a peak of about 2 at the beginning of 2017 (Fig. 4b) and a sharp decline shortly after. The average of R_t over weeks 40 to 55 (the same time interval used to estimate the epidemic growth rate) provides a consistent alternative estimate for R_e of 1.60 (95%CI: 1.23–2.04).

4. Discussion

In this work, we estimated the generation time of HAV using a Bayesian method for the reconstruction of transmission links within households with multiple cases, using data from a major outbreak of AHA occurred in the Lazio region (Lanini et al., 2017) genetically linked to the epidemics that was ongoing throughout Europe in the same period (European Centre for Disease Prevention and Control, 2018). Although reconstruction of transmission events is always a challenge prone to mistakes, we found that the source of infection was robustly inferred for the majority of cases transmitted within households. Transmission chain reconstruction remained undetermined for 25 of 103 considered cases, i.e. mostly for cases for which the serial interval from other cases was within four days (Fig. 1). In these cases, it was not possible to discriminate whether both cases were exposed to the same source at the same time outside the household or if either patient acquired infection first and then infected the other. These results underline that during a wide epidemic involving a large metropolitan area where people move for long stretches, it is possible that even for cases within the same household, the potential source of exposure may be diverse. For 13 cases, serial interval from the household index case was longer than three months. All these cases were classified by the model as independent viral acquisition from outside the household. Alternative explanations for such long serial intervals might be

Table 1
Main demographics of cases, for the overall epidemic and for all households with multiple infections.

Age/sex	Overall epidemic			Households		
	M (%)	F (%)	Tot (%)	M (%)	F (%)	Tot (%)
0–15 (children)	24 (2.7)	16 (15.5)	40 (4.0)	11 (10.7)	5 (4.8)	16 (15.5)
16–30	275 (30.8)	25 (24.3)	300 (30.0)*	32 (31.1)	4 (3.9)	37 (35.9)**
31–45	432 (48.4)	28 (27.2)	460 (46.1)	26 (25.2)	7 (6.8)	33 (32.0)
> 46	161 (18.0)	34 (33.0)	195 (19.5)	12 (11.7)	5 (4.9)	17 (16.6)
Total	892* (89.4)	103* (10.3)	998 (100.0)	81** (78.6)	21** (20.4)	103 (100.0)

* Two individuals in age group 16–30 had unspecified sex and 1 male had unspecified age.
** One individual in age group 16–30 had unspecified sex.

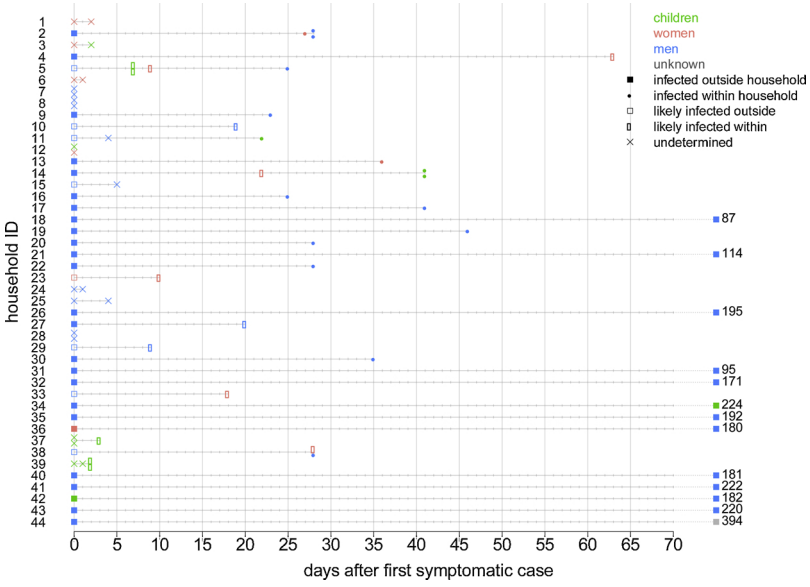

Fig. 1. Schematic representation of the 103 cases belonging to 44 households with multiple infections. Cases with symptom onset later than 70 days since the first symptomatic case are reported on the right-hand side of the graph and the number represents the relative time of symptom onset in days. When two cases have the same date of symptom onset within a household, they are reported as two distinct points, one above and one below the corresponding household timeline. "Likely" refers to a consistent classification over at least 75% of the reconstructed transmission chains. "Undetermined" indicates a classification that was not consistent in at least 75% of chains; all other data points (represented with filled dots) indicate a consistent classification over all chains.

either the presence of an undetected (asymptomatic) infector or a relapse of infection, which occurs in 10–15% of cases within 6 months from initial infection (Lanini et al., 2018; European Centre for Disease Prevention and Control (ECDC), 2016). In particular, the presence of high rates of asymptomatic infections in children below 6 years (Lanini et al., 2018) may be a source of bias for the reconstruction of transmission events concerning this age group. Despite these limitations, the average estimated value of the generation time was consistent with available estimates of the average serial interval (Simpson, 1948; Brodribb, 1952), supporting the correct identification of its probability distribution from household transmission events.

The reconstructed transmission events showed that there was a significant HAV spillover from the general outbreak to households, differently from what has been found for other European countries (Friesema et al., 2018). Children and women represented 31% (32/103) of AHA cases within households with multiple cases, against only 11% (95/892) of the remaining cases. According to our reconstructed transmission links, most children and women in households with multiple AHA cases were infected within the household, and the majority of men outside of it. Proof of spillover clusters of transmission among non-MSM within the Lazio outbreak was previously provided by molecular analyses on a subset of cases (Lanini et al., 2017).

From the distribution of the generation time, we obtained an estimate of the reproduction number during the considered HAV outbreak. We found an R_e of 1.63 (95%CI 1.35–1.94), which is slightly lower than

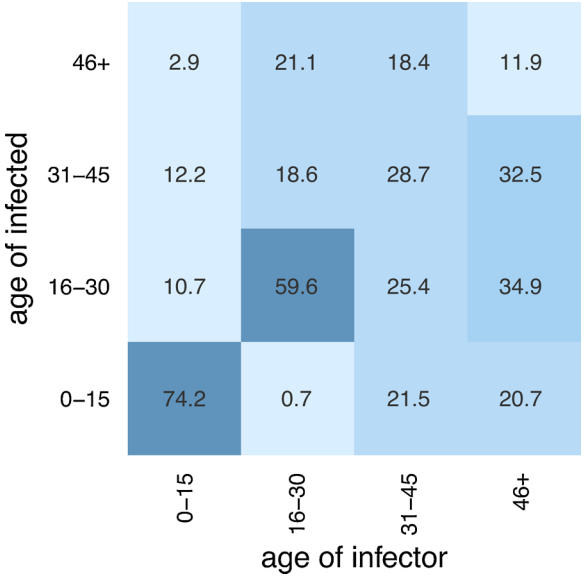

Fig. 3. Matrix of reconstructed transmission links within households with multiple AHA cases, by age; numbers refer to the relative percentage of transmission events from an infector of a given age group to the age group of the infected (i.e., each column sums up to 100%).

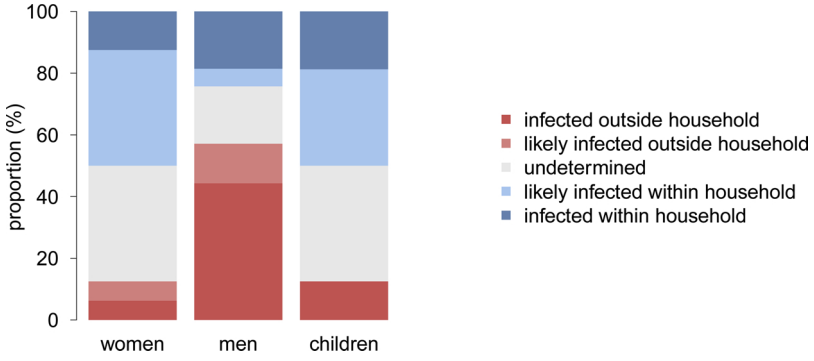

Fig. 2. Model classification on the source of infection for households with multiple AHA cases. Men: males above 15 years old; women: females above 15 years old; children: individuals of any sex of age 15 or lower.

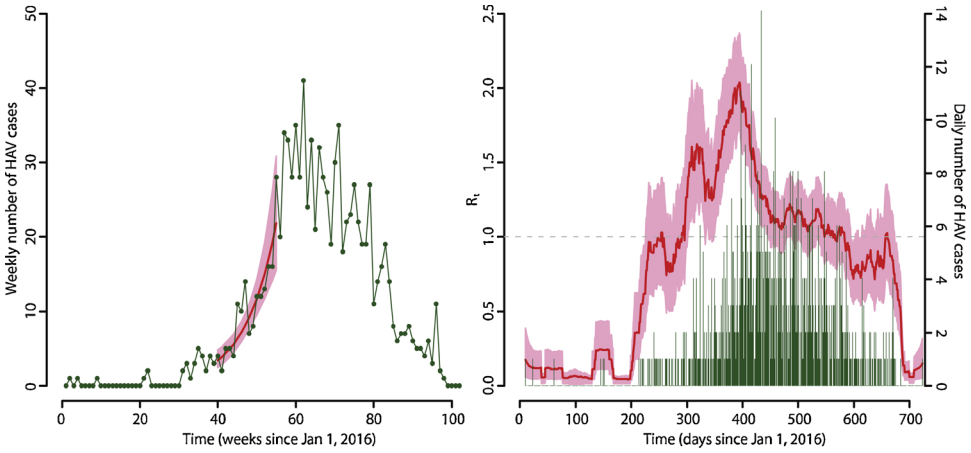

Fig. 4. a) Weekly number of HAV cases (green line) in the overall outbreak and fit of the curve in the exponential growth window (weeks 40–55 since January 1st, 2016; red line: mean; shaded area: 95%CI). **b)** Daily number of HAV cases (green bars) in the overall outbreak and estimate of the instantaneous reproduction number from the renewal equation (red line: mean; shaded area: 95%CI).

estimates found in other outbreaks among MSM in settings with similar epidemic patterns such as Australia (range 1.71–3.67 (Regan et al., 2016)) or in endemic settings such as in data from United Kingdom during the 1980s (range 1.6–2.2) (Gay et al., 1994). In particular, during the Lazio outbreak, the instantaneous reproduction number peaked at about 2 at the beginning of 2017 and declined rapidly thereafter, presumably as a consequence of vaccination and awareness campaigns started in February. Indeed, the epidemic curve peaked in March 2017 and a first trend decline was appreciated since April 2017, confirmed in the following months. However, interventions were not able to reduce the instantaneous reproduction number below the epidemic threshold until the second half of 2017.

Our estimate for the reproduction number suggests that about 50% ($1–1/R_0$) of the at-risk persons should be immunized to prevent large outbreaks. Indeed, immunization of exposed persons has been shown to be effective in reducing HAV transmission (Lanini et al., 2018). WHO suggests that HAV vaccination should be tailored on specific local epidemic profiles. In particular, targeting special populations may be the best intervention in high-income countries where AHA occurs as sporadic cases in travelers, small clusters in closed and semi-closed communities (e.g. PWID, MSM) and among children in schools (Lanini et al., 2018). The identification of spillover via household contacts in the Lazio outbreak confirms the opportunity of targeting household members of infectious cases. Notably, during the 2016–2017 European outbreak, the limited availability of vaccines has slowed down the implementation of prevention campaigns, with nine countries (including Italy) reporting some degree of shortages in vaccine stockpiles (European Centre for Disease Prevention and Control, 2018). Logistic issues related to the management of vaccine procurements need therefore to be taken into account.

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Declaration of interests

None.

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