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# Hepatitis C Outbreak in Haemato-Oncology Ward: A Challenge of Investigating the Transmission Mechanism in Patients with Multiple Exposures

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**Abstract**

**Background:** Nosocomial transmission of Hepatitis C Virus (HCV) continues to occur, even in developed countries. Recent HCV outbreaks most often concern vulnerable populations, such as patients of haemodialysis units, oncology wards and CT/MRI scanning units. We report an investigation of an outbreak in haemato - oncology ward to determine transmission mechanisms and to discuss challenges arising in these settings.

**Methods:** We include as cases previously undiagnosed HCV infected patients, hospitalized in the haemato-oncology ward between 1st August and 31st October with outbreak strain confirmed with Next-Generation Sequencing (NGS) analysis of Hypervariable Region 1 (HVR1). The required similarity threshold for outbreak strain was 3.7% genetic distance. We selected the exposure period based on HCV incubation time, due to multiple hospitalizations of all patients in the implicated ward. We attempted to screen all patients hospitalized during exposure period and collected exposure data from medical records.

**Results:** Of 129 people eligible for screening, 34 died before being reached, 17 refused or could not be contacted, and 78 were tested. HCV infection was confirmed (HCV-RNA) in 11 (14%) patients, of whom in seven HVR1 amplification was feasible and all harboured the outbreak strain. Reception of chemotherapy in August 16-31 (AOR 30.17, 95% CI 2.45-371.21) and in October 1-15 (35.09, 2.53-487.28) was significantly associated with infection. Infected batches were excluded as source since patients received different regimens. However, minor procedures, such as i.v. line flushing, were not fully documented. Multidose vials of saline were used.

**Conclusion:** Our results indicate a close relationship of the virus in the haemato-oncology ward patients suggesting a common source of infection, despite inconclusive exposure analysis. Plausible transmission route includes breaches in minor procedures. As HCV outbreak investigations inevitably rely on medical documentation, we recommend that at least those minor procedures, which were previously linked to transmission, be documented in detail.

**Keywords:** HCV; Hepatitis C; Healthcare associated infections; Infection transmission; Molecular epidemiology

## Introduction

European surveillance data attribute the majority of newly diagnosed Hepatitis C (HCV) infections to injecting drug use. Likewise, people who inject drugs constitute the most affected group in the European countries [1–3]. Nonetheless, a substantial proportion of HCV cases do not report injecting drug use. While some of the cases, especially among men who have sex with men appear to be transmitted sexually, many report only exposures to medical invasive procedures. Although infrequent in developed countries, health-care related transmission risk still persists despite elimination of the risk associated with blood transfusions [4,5] and it may be especially relevant to patients with conditions requiring frequent medical interventions, in populations with higher background prevalence such as patients of haemodialysis units or diabetes patients [4,6,7]. Infections occur in relation to breeches in safety procedures or implementation of inadequate procedures, notably during unsafe injections [4].

In Poland the surveillance data indicate that the past or current transmission related to medical procedures continues to impact the current hepatitis C burden. This is confirmed by seroprevalence and case-control studies identifying transfusion before 1992 as the key risk factor for prevalent cases. Other risk factors include multiple hospitalizations and minor medical procedures. The association with particular procedures is not consistent across studies, drawing attention to the fact that different medical procedures may be involved in different populations [8–10]. Furthermore, medical procedures, especially minor medical and dental procedures tend to still contribute to the spread of the HCV infection in Poland [11–13].


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**Table 1:** Minimal pairwise distance between viral strains isolated from patients and from controls.

| Minimum pairwise distance | Patient code | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient code | **Pt_02** | **Pt_03** | **Pt_04** | **Pt_05** | **Pt_06** | **Pt_07** | **Pt_08** | **C_11** | **C_14** | **C_16** | **C_52** | **C_56** | **C_93** | **C_110** | **C_114** | **C_118** |
| Pt_03 | 0,6% | | | | | | | | | | | | | | | |
| Pt_04 | 0,0% | 0,6% | | | | | | | | | | | | | | |
| Pt_05 | 0,0% | 0,6% | 0,0% | | | | | | | | | | | | | |
| Pt_06 | 0,6% | 1,3% | 0,6% | 0,0% | | | | | | | | | | | | |
| Pt_07 | 0,6% | 1,3% | 0,6% | 0,0% | 0,0% | | | | | | | | | | | |
| Pt_08 | 0,6% | 1,3% | 0,6% | 0,0% | 0,0% | 0,0% | | | | | | | | | | |
| C_11 | 17,4% | 18,2% | 17,3% | 16,7% | 18,2% | 18,2% | 12,7% | | | | | | | | | |
| C_14 | 17,4% | 17,7% | 17,3% | 16,7% | 18,2% | 18,2% | 9,7% | 0,0% | | | | | | | | |
| C_16 | 17,8% | 17,8% | 16,8% | 17,0% | 18,6% | 18,6% | 11,9% | 0,0% | 0,0% | | | | | | | |
| C_52 | 18,5% | 18,5% | 18,4% | 17,7% | 19,3% | 19,3% | 12,6% | 11,3% | 10,3% | 0,0% | | | | | | |
| C_56 | 20,2% | 20,2% | 20,2% | 19,4% | 20,2% | 20,2% | 13,6% | 14,5% | 12,7% | 15,8% | 15,0% | | | | | |
| C_93 | 17,4% | 17,4% | 16,8% | 16,7% | 18,2% | 18,2% | 9,7% | 0,0% | 0,0% | 0,0% | 9,7% | 12,7% | | | | |
| C_110 | 18,3% | 19,1% | 18,3% | 17,5% | 19,1% | 19,1% | 15,2% | 13,4% | 12,7% | 14,3% | 15,0% | 14,6% | 12,7% | | | |
| C_114 | 20,9% | 20,9% | 20,9% | 20,1% | 21,8% | 21,8% | 14,3% | 12,1% | 12,1% | 16,6% | 15,8% | 11,2% | 12,6% | 16,1% | | |
| C_118 | 16,1% | 15,3% | 15,2% | 15,3% | 15,3% | 15,3% | 0,0% | 12,0% | 11,0% | 11,1% | 12,6% | 13,6% | 11,0% | 16,1% | 13,5% | |
| C_120 | 19,3% | 20,1% | 19,1% | 18,5% | 18,5% | 18,5% | 16,0% | 11,1% | 11,1% | 13,5% | 13,5% | 17,7% | 11,1% | 13,5% | 16,0% | 15,2% |

The number of base substitutions per site from between sequences are shown. Analyses were conducted using the Maximum Composite Likelihood model [40]. The analysis involved 77 nucleotide sequences. Codon positions included were 1st+2nd+3rd+ Noncoding. All positions containing gaps and missing data were eliminated. There were a total of 155 positions in the final dataset. Evolutionary analyses were conducted in MEGA5 [25].

Occurrence of nosocomial outbreaks may be also considered as an indicator of recent transmission events, for which the actual transmission mechanism could be identified. In a review carried out in the United States a substantial number of HCV outbreaks was identified in outpatient settings, particularly in haemodialysis centres, but also in hematology/ oncology and pain remediation clinics [6]. Similar HCV outbreaks have been also reported in Europe. In the published literature, the most commonly reported hepatitis C outbreaks in Europe concern haemodialysis units, oncology wards and CT/MRI scanning units [14].

Outbreak investigations in case of HCV infection can pose different methodological challenges. Due to predominantly asymptomatic course of disease, it is very likely that many outbreaks, especially smaller ones, are not identified. Moreover, as cases are usually diagnosed with delay, the confirmation of a link between cases is not evident, unless genetic identification of the outbreak strains is performed. The genetic analysis is complicated by existence of multiple quasi-species within one host [15], given documented possibility of transmission of minority variants [16]. Next Generation Sequencing (NGS) - based variant analysis allows to resolve this difficulty [16,17].

We report an outbreak among haemato-oncology patients in a county hospital in Poland. The suspected outbreak was reported in December 2015 to local public health department, with five cases initially diagnosed among patients of haemato-oncology ward. In addition to investigation of the possible transmission mechanisms, we aim to discuss technical difficulties arising in these settings.

## Methods

### Initial information and the exposure period

At the time of the outbreak, report five patients (confirmed HCV-RNA) have already been diagnosed in the ward, two of whom developed jaundice and three tested due to high levels of ALT. The first patient was diagnosed in October, the second in November and the other three in December. Initially local clinicians suspected exacerbation of chronic HCV infection due to chemotherapy [18], which caused the delay in reporting of the outbreak. The possibility of reactivation was later excluded as the patients did not receive the implicated chemotherapy regimens and earlier HCV infection was not documented in any of the five patients [19]. The review of surveillance data at local and regional level identified additional two cases of acute hepatitis C (both were diagnosed because of jaundice) that reported hospitalization in the implicated ward, notified in December 2015 and January 2016. They also negated other major HCV exposures (injecting drugs, tattooing), although one patient also reported hospitalization in a different hospital. In order to identify the possible exposure time we aligned the hospitalization times of all patients. All of them were admitted in the implicated ward multiple times in 2015 and were hospitalized in August 2015, but no single day could be identified when all were present. Moreover, August would fall out of the typical incubation period for acute hepatitis C (3-12 weeks, on average 7 weeks) [20]. We considered, that there could be more than one transmission event or some of the cases could be unrelated to the outbreak. In addition, longer incubation time due to underlying disease or chemotherapy could be taken into account. It was shown that time to HCV seroconversion is longer in patients with haematological disorders [21,22].

Initially, we selected the presumed exposure period based on HCV incubation time and extended it to account for the period when they were all hospitalized. Finally, the exposure period encompassed the time between August 1st and October 31st.

**Table 2:** Distribution of medical exposures among HCVRNA negative controls, probable and confirmed and confirmed cases only.

| | | HCVRNA negative controls | Probable and confirmed cases | Confirmed cases |
|---|---|---|---|---|
| | | N(%) | N(%) | N(%) |
| Total | Total | 67 (100.0) | 10 (100.0) | 7 (100.0) |
| | | | | |
| Hospitalised in Aug 2015 | No | 28 (41.8) | 1 (10.0) | 0 (0.0)* |
| | Yes | 39 (58.2) | 9 (90.0) | 7 (100.0) |
| | | | | |
| Hospitalised in Sep 2015 | No | 41 (61.2) | 3 (30.0) | 2 (28.6) |
| | Yes | 26 (38.8) | 7 (70.0) | 5 (71.4) |
| | | | | |
| Hospitalised in Oct 2015 | No | 52 (77.6) | 3 (30.0)** | 1 (14.3)** |
| | Yes | 15 (22.4) | 7 (70.0) | 6 (85.7) |
| | | | | |
| Received chemotherapy a biopsy in Aug-Oct 2015 | No | 43 (64.2) | 3 (27.3)* | 0 (0.0)** |
| | Yes | 24 (35.8) | 8 (72.7) | 7 (100.0) |
| | | | | |
| Underwent a biopsy in Aug-Oct 2015 | No | 51 (76.1) | 8 (72.7) | 6 (85.7) |
| | Yes | 16 (23.9) | 3 (27.3) | 1 (14.3) |
| | | | | |
| Underwent a trepan biopsy in Aug-Oct 2015 | No | 59 (88.1) | 11 (100.0) | 7 (100.0) |
| | Yes | 8 (11.9) | 0 (0.0) | 0 (0.0) |
| | | | | |
| Underwent CT/MR scan with contrast in Aug-Oct 2015 | No | 58 (86.6) | 9 (81.8) | 6 (85.7) |
| | Yes | 9 (13.4) | 2 (18.2) | 1 (14.3) |
| | | | | |
| Had a transfusion in Aug-Oct 2015 | No | 60 (89.6) | 5 (45.5)** | 4 (57.1)* |
| | Yes | 7 (10.4) | 6 (54.5) | 3 (42.9) |
| | | | | |
| I.V. line placement in Aug-Oct 2015 | No | 8 (11.9) | 0 (0.0) | 0 (0.0) |
| | Yes | 59 (88.1) | 11 (100.0) | 7 (100.0) |
| | | | | |
| | | | | |
| Subcutaneous fraxiparine administration in Aug-Oct 2015 | No | 55 (82.1) | 9 (81.8) | 5 (71.4) |
| | Yes | 12 (17.9) | 2 (18.2) | 2 (28.6) |
| | | | | |
| Catheter placement in Aug-Oct 2015 | No | 67 (100.0) | 10 (90.9) | 6 (85.7) |
| | Yes | 0 (0.0) | 1 (9.1) | 1 (14.3) |
| | | | | |
| Insulin administration by pen in Aug-Oct 2015 | No | 64 (95.5) | 11 (100.0) | 7 (100.0) |
| | Yes | 3 (4.5) | 0 (0.0) | 0 (0.0) |
| | | | | |
| Procedures outside of the implicated ward in Aug-Oct 2015 | No | 61 (91.0) | 7 (63.6)* | 4 (57.1)* |
| | Yes | 6 (9.0) | 4 (36.4) | 3 (42.9) |
| | | | | |
| Total hospitalization length in Aug-Oct 2015 in days | mean (SD); median [range] | 5.8 (0.6); 4 [1-29] | 23.3 (4.9); 23 [6-65]*** | 25.4 (7.4); 23 [6-65]*** |

### Case definitions

The initial case definition for screening purposes was a previously undiagnosed HCV infected (confirmed by HCV-RNA test) patient, hospitalized in the haemato-oncology ward during the specified exposure period (August 1st and October 31st 2015).

The case definition used for analysis in addition included the results Next-Generation Sequencing (NGS) analysis of Hypervariable Region 1 (HVR1). The case was classified as probable if there was no sample available for genetic analysis or the HCV strain could not be isolated. A patient meeting the screening case definition was considered to be a confirmed outbreak case if at least one of the strains isolated from this individual had a genetic distance of less than 3.7% from at least one variant strain from another patient, i.e. the minimum pairwise distance was less than 3.7%. This criterion was suggested in prior review work [16].

We further supported the selection of the cases possibly from a single transmission event by comparing genetic distances observed between the control sequences and between the case and control sequences.

### Data and sample collection

We screened all patients hospitalized during specified exposure period and collected exposure data from medical records. The patients were invited to take part in the investigation, when returning to the hospital for next cycles of chemotherapy or control visits. The remaining patients were contacted at their home address. The patients were offered HCV screening, and a venous blood sample was collected from those who gave their consent. The samples were processed in the hospital laboratory and the sera were frozen and shipped to National Institute of Public Health – National Institute of Hygiene and the Warsaw Medical University for testing. The medical record of the patients were reviewed for all medical procedures associated with possible percutaneous exposure that took place during the exposure period. Based on these data a questionnaire to extract data from other patients records was constructed. All cases were also interviewed with routine surveillance questionnaire comprising also life-style exposures.

We used 10 samples from unrelated acute hepatitis C identified in blood donation service as control samples for molecular characteristics of the HVR1 region of the virus.

### Laboratory methods

Next-Generation Sequencing (NGS) analysis of Hypervariable Region 1 (HVR1) was used to search for relatedness of HCV variants as described in [23].

In brief, total RNA was extracted from 250 µl of serum using Trizol (Life Technologies, Carlsbad, CA, USA) and subjected to reverse transcription using AccuScript High Fidelity Reverse Transcriptase (Agilent Technologies, Santa Clara, CA, USA) and random hexamers. A region of 175 nt length encompassing HVR1 was amplified in two-step PCR using FastStart High Fidelity Taq DNA Polymerase (Roche, Indianapolis, IN, USA) using sequence-specific promers. Primers employed in the second PCR contained tags recognized by GS Junior sequencing platform, standard 10-nucleotide multiplex identifiers and target-complementary sequence. Approximately 3×107 DNA amplicons were subjected to emulsion PCR using the GS Junior Titanium emPCR Lib-A Kit (454 Life Sciences, Branford, CT, USA). Amplicons were sequenced according to the manufacturer's protocol using GS Junior platform (454 Life Sciences). HVR1 variants were reconstructed using the program diri_sampler from the Shorah software suite [24]. Subsequently, reconstructed haplotypes of frequency >0.5% were aligned by MEGA (Molecular Evolutionary Genetics Analysis), version 6.0 (http://www.megasoftware.net/) [25].

### Statistical analysis

Fisher exact test was used to compare distribution of categorical covariates between cases and controls. Medians of numerical variable were compared with Mann-Whitney test. We used logistic regression to estimate the odds ratio of being a confirmed outbreak case as compared to HCV-RNA negative patients. Due to small sample size we were not able to study the full multivariate model. We investigated the predictors important in univariable analysis in pairs to identify the strongest ones. For factors (exposures) perfectly predicting the outcome the separate indicator variables were created to describe whether the exposure occurred in August, in September or in October.

## Results

Of 129 people eligible for screening, 34 died before being reached, 17 refused or could not be contacted, and 78 were tested. HCV infection was confirmed in 11 (14%) patients, of whom in seven HVR1 amplification was feasible.

### NGS results and case classification

NGS analysis revealed intrahost variability of HVR1 both in the samples from examined patients and the control samples from acute HCV infections identified in blood donors. Among the seven patients the predominant strain accounted for 54.1% - 100% of frequency of all strains identified and among the controls the predominant strain accounted for 32.6%-97.6% of frequency. The pairwise minimal distances between the cases meeting the screening definition varied between 0.0% and 1.3%, while between patients and controls they remained between 9.7% - 21.8% (apart from one 0.0% distance, between Pt_8 and C_118) and between controls – 0.0% - 16.6% (Table 1). The minimal distances between the strains isolated from the patients coincided with the distances between the predominating strains. The patient Pt_8 harboured three unrelated strains, one of which was similar to the strains isolated from other cases (minimal pairwise distances from 0.0% to 1.3%). Another strain, with relative frequency of 3%, was closely related (0.0% distance) to the strains isolated from the control C_118. The minimal distances between the strains isolated from controls related to minority strains. Distances between the predominating strains exceeded 10%.

Based on this analysis the seven patients will be considered confirmed outbreak cases with possible single source infection. The four patients either for whom no samples were available or no amplification was achieved were classified as probable cases.

### Patient characteristics

The proportion of females among the uninfected individuals, all HCV-RNA positive cases and confirmed outbreak cases was, 64.2% (43/67), 45% (5/11) and 42.9% (3/7), respectively, and the mean (median) age in years – 64.9 (67), 60.7 (64) and 64.7 (66), respectively.

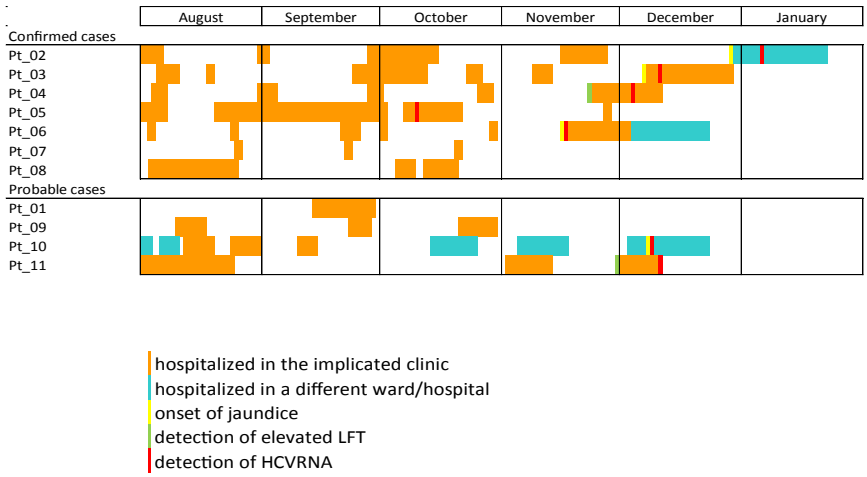


**Figure 1:** Summary of the exposure in the health care and HCV diagnosis among confirmed and probable outbreak case 1.

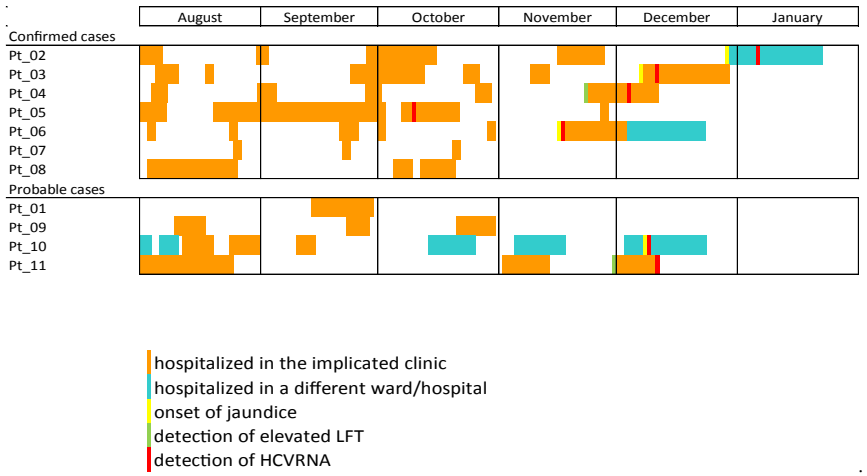


**Figure 2:** Summary of the exposure in the health care and HCV diagnosis among confirmed and probable outbreak case 2.

The most common clinical diagnosis related to hospitalization were lymphoma (20.5%), multiple myeloma (20.5%) and leukemia (17.9%). Other diagnoses included thrombocytopenia, anaemia, polyglobulia, myelodysplasia, monoclonal gammopathy. The distribution of main diagnoses was not significantly different between cases and controls (p=0.323).

Altogether four patients developed jaundice and only two seroconverted at the time of sample collection (Pt_3, Pt_9). In case of one patient (Pt_11) clinical history and the sample were not available. All patients were hospitalized multiple times during the presumed exposure period (Figure 1,2).

## Exposure analysis

The overall hospitalization time during the exposure period (August – October 2015) was significantly longer among cases than among the uninfected patients hospitalized during the exposure period. Consequently, cases were more likely to be hospitalised in each of the examined months (Table 2). Significantly more cases than controls received chemotherapy, or blood transfusion or were subjected to a procedure outside of the implicated ward. Further investigation revealed that cases had different blood groups, excluding blood transfusion as a likely source of infection. Moreover, the category "procedures outside of the implicated ward" included different procedures performed in different medical facilities.

We further investigated the length of hospital stay and receiving the chemotherapy as the main risk factors for infection. We analysed the total lengths of hospital stay as well as the number of days spent in the implicated ward in August, September and October. All cases were hospitalized in August so the number of days in August was split into number of days in the August 1 – 15 and in August 16 – 31 to avoid perfect prediction problem. Similarly, all cases received chemotherapy and this variable was split into chemotherapy in August 1 -15, chemotherapy in August 15 -31, in September and in October. Increasing length of hospitalization predicted increased odds of infection (Table 3). When investigating the length of stay in August, September and October as separate variables in one model the length of stay in September was not significant, however both the number of hospitalization days in August and in October were significantly associated with HCV infection with an outbreak strain (AOR for each additional day in August 1.3, 95% CI 1.07-1.58 and for

**Table 3:** Exposures associated with infection, by month (or half-month) of exposure.

| | OR* | 95% CI | p-value | AOR** | 95% CI | p-value |
|---|---|---|---|---|---|---|
| Duration of hospitalization in the implicated ward | | | | | | |
| Total number of days Aug - Oct | 1.23 | 1.09-1.39 | 0.001 | | | |
| Number of days Aug | 1.28 | 1.08-1.52 | 0.004 | 1.30# | 1.07-1.58 | 0.008 |
| Number of days Sep | 1.17 | 1.01-1.35 | 0.033 | | | |
| Number of days Oct | 1.31 | 1.12-1.54 | 0.001 | 1.36# | 1.09-1.7 | 0.006 |
| | | | | | | |
| Reception of chemotherapy | | | | | | |
| Aug 1-15 | 5.05 | 1.01-25.22 | 0.049 | | | |
| Aug 16-31 | 44.25 | 4.7-416.53 | 0.001 | 30.17## | 2.45-371.21 | 0.008 |
| Sep | 9.83 | 1.85-52.19 | 0.007 | | | |
| Oct | 31 | 4.75-202.34 | <0.001 | | | |
| Oct 1-15 | 39.38 | 5.74-270.25 | <0.001 | 35.09## | 2.53-487.28 | 0.008 |
| Oct 16-31 | 28.44 | 4.29-188.75 | 0.001 | | | |

a day in October – 1.36, 95% CI 1.09-1.7). Receiving chemotherapy in either of the analysed time periods increased odds of infection, with the largest effect sizes for the August 16-31 and October, which was also split to October 1-15 and October 16-31 (Table 3). When analysing these variables in pairs, two significant independent effects emerged – reception of chemotherapy in August 16-31 (AOR 30.17, 95% CI 2.45-371.21) and in October 1-15 (35.09, 2.53-487.28).

### Additional information

Closer investigation in the chemotherapy procedures revealed that the outbreak cases were administered different regimens and the chemotherapy preparation was under strict control. This is therefore unlikely that a contaminated batch of chemotherapy drugs could be the source of this outbreak. The cases received chemotherapy on different days, with some overlaps. On the overlapping days often they were treated in different rooms. There was a common preparation area, where auxiliary drugs were prepared.

Minor procedures (e.g. i.v. line flushing, injections) were not fully documented. In e.g. the information was available on placement of an i.v. line, but not about the line care. Multi-dose vials of saline in 100ml containers were used to flush the ports. No syringe re-use was reported.

### Actions taken by the hospital

In response to the outbreak the hospital undertook actions to enhance universal precautions with their staff. They also implemented anti-HCV screening at admittance to identify potential chronic infections. Moreover, the multi-dose vials were replaced by single dose vials in this ward.

## Discussion

We identified an HCV outbreak in hospital settings confirmed by close genetic relation of the viral strains isolated from the cases. The analysis of exposures points to association of the outbreak with reception of chemotherapy, although the minor procedures performed in relation to chemotherapy administration could be the most likely mechanism of transmission. Two periods are independently associated with infection risk. This implies that the outbreak consisted of at least two transmission events.

Existence of two or more transmission events is also supported by comparing the onset time in symptomatic cases to the diagnosis time in the first diagnosed patient (Pt_05). While an average incubation time for the symptomatic cases implies that transmission could occur in October/November, the first patient was already diagnosed before that time. The likely scenarios include several introductions from the same source-patient or sequential transmission from one patient to another. None of the tested individuals was diagnosed with HCV before. Among the outbreak cases only one had seroconverted by the time of sample collection and this case presented with clinical picture of acute hepatitis C. In the immunocompromised patients seroconversion may be delayed despite ongoing infection [22,26]. However, that should not affect a chronic infection established prior to the hematologic disorder or oncologic treatment. We therefore conclude that the outbreak cases were all acute infections and we did not identify the presumed source patient with chronic infection. This could be expected given that a substantial proportion of the possibly exposed population was not available for screening.

The association of the outbreak strain infection with the number of days of the hospital stay could suggests a repeated or even systematic problem in applying the universal precautions. Neither the hospital infection team nor the outbreak team convened by the local State Sanitary Inspection office was able to identify such procedure. Given the limited number of cases we were not able to study the independent effects of being hospitalized on each particular day, thus the association with the longer hospital stays may also indicate the likelihood of being present on the particular day or days when the transmission event occurred.

Exposure analysis revealed that receiving chemotherapy, especially during one of the implicated time periods was the only factor associated with the risk of infection, that could not be ruled out as contributing to the outbreak. Even if the preparation of chemotherapy was under strict control and fully documented, the minor procedures associated with chemotherapy administration were not. As the cases were administered the chemotherapy in different rooms the supposed

breach could occur in medication preparation area, where the only risk factor identified were the multi-dose vials. The link with minor procedures remains hypothetical. However, given the close genetic relation of the HCV strains isolated from the patients and exclusion of other infection mechanisms strongly indicates this transmission route. Moreover, no more cases were identified after enhancement of universal precautions and discontinuation of multi-dose vial use.

Multiple viral outbreaks among patients of oncology and hematology wards have been reported in the literature. The higher prevalence of blood-borne pathogens among patients of such wards may be a contributing factor. HCV infections generally tend to be more prevalent in patients with hematologic malignant diseases as there exists the causative link between HCV and development of certain types of non-Hodgins lymphomas [27]. The transmission routes of the outbreaks quite often are difficult to establish [28–31], but if the mechanisms are clarified, they are most often related to minor procedures, such as syringe reuse or contaminated multi-dose vials, especially used for flushing of catheters or i.v. lines [32–34]. In general, breaches in minor procedures have been implicated in multiple health care related outbreaks [5,30,32,35–37], often linked to sharing vials for several patients or inappropriate environment and hand hygiene. In our report contaminated multi-dose vials remain the most plausible transmission route. Accidental contamination from the surface cannot be excluded, even though clean areas for medication preparation were separated. HCV is able to survive on inanimate surfaces for prolonged time [38], but correct use of antiseptics reduces infectivity to undetectable levels [39]. As the HCV outbreak investigations take place after prolonged time from the exposure proving or disproving surface contamination as source of outbreak was not feasible. Nonetheless, strict adherence to universal precautions and workflow organisation that minimizes the risk of human error should be implemented. Multi-dose vials should be discouraged, especially in the settings where there is higher prevalence of infection among the patient group served, even if safety devices are used.

Finally, we note that the outbreak was identified and investigated with a substantial delay. There were no procedures in place for notification and screening of potentially exposed patients and nearly 40% of the patients could not be reached. Majority of them have died due to their oncologic condition, still analysing their samples and the clinical history would have improved the statistical power to identify the transmission mechanism. Moreover, we may have underestimated the final size of the outbreak, as asymptomatic infections could have occurred in the group that was not screened. Incomplete documentation of the minor invasive procedures constituted another difficulty.

## Conclusion

Our results indicate a close relationship of the virus in the haemato-oncology ward patients suggesting a common source of infection, even though we were not able to fully identify the transmission mechanism. Plausible transmission route includes breaches in minor procedures related to chemotherapy administration and possibly more than one transmission event occurred. As HCV outbreak investigations inevitably rely on medical documentation, we recommend that at least those minor procedures, which were previously linked to transmission, should be documented in detail. Moreover, we note that the investigation was delayed due to difficulties with blood collection from the exposed patients. Procedures on epidemiological management of acute hepatitis C should include sample collection and immediate notification to the local public health departments.

Finally, HCV outbreaks are usually small and dispersed in time, thus molecular analysis, especially with variant analysis is crucial to confirm them.

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