Screening of Spill and Leakage of Antibiotics in Hospital Wards

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Screening of spill and leakage of antibiotics in hospital wards

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Abstract

This paper presents a two-phase study of spill and leakage of antibiotics in hospitals. The first phase was a screening of spill and leakage at 21 hospital wards in 16 hospitals. Phase two was an extended investigation where different measures to reduce spill and leakage were implemented and a follow-up screening was made to evaluate the effect of the measures. At the screening, 206 samples were collected. The result was used to classify the wards into four classes: *Low*, *Mean*, *High* and *Very high*. Spatial distribution patterns and the effect of compounding systems were also investigated. The screening showed that spill and leakage occur at all wards. Eleven of the 21 wards had *High* or *Very high* contamination level. This result also showed that the substances were distributed according to three possible patterns. The compounding systems also had an impact on the spill and leakage. All four wards that used closed system were found among the six wards with the lowest spill and leakage, while all three wards that used open venting systems were found among the six wards with the highest spill and leakage. The result also showed that it is possible to handle antibiotics with only insignificant spill and leakage, i.e., by using closed systems. Three wards, classified as *Very high*, were included in the second phase. Measures to decrease spill and leakage and reduce the distribution the substances were implemented. After two month, a follow-up screening was carried out. The result showed lower contamination levels at all three wards and the implemented measures had some effect. Simple and easy-to-do measures can contribute to reduce the spill and leakage that occur. There is still, however, a need to discuss how to handle antibiotics in a safe way to reduce possible spill and leakage and to prevent the distribution of this spill and leakage.

Key words

Antibiotics, compounding, hospital wards, leakage, occupational exposure, screening, spill, surface contamination, wipe sampling

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Introduction

During the past fifteen years, there are many studies published that describe monitoring methods and/or investigations of spill and leakage and/or occupational exposure to antineoplastic drugs. A comprehensive web based database with reference to literature on this topic has been compiled by Dr Tom Connor at National Institute for Occupational Health (NIOSH) in the US [1]. Although most countries have strict regulations for handling antineoplastic drugs [2-5], these studies show that spill and leakage frequently occur during handling these drugs in hospital wards and in pharmacies. Moreover, the studies show that the staff gets undesired exposure to these drugs.

Antibiotics can be regarded as another heterogenic group of drugs that is frequently used in hospitals. Over 140 times more antibiotics compared with antineoplastic drugs are administered to hospital patients in Sweden [6] and there are only limited regulations for safe handling of antibiotics in medical care, compared with the situation for antineoplastic drugs. It is therefore not unrealistic to assume that the spill and leakage of antibiotics are the same or larger than with antineoplastic drugs.

There are some reviews on analytical methods for antibiotic substances for pharmacokinetic studies and for antibiotic residues in foodstuffs [7-8]. There are also several studies on the distribution of drugs in the environment through sewer effluents [9-12]. Tuerk *et al* [13] has compared different analytical methods for determination of antibiotic substances in environmental and biological samples. There are, however, almost no studies on spill and leakage of antibiotics in medical care.

There have been two main purposes of this study. The first aim has been to investigate the spill and leakage of antibiotics in Swedish hospitals using a previously developed and validated screening method [14]. The method is based on wipe sampling and liquid chromatography tandem mass spectrometry (HPLC-MS/MS) for determination of sampled antibiotics. Twelve different antibiotics have been analysed in over 200 samples collected in 21 wards at 16 different hospitals.

The second aim has been to identify measures to reduce the spill and leakage of antibiotic drugs. In a deeper study at three wards, a number of possible preventive measures were identified and suggested to the wards. After some time for implementation, a follow-up screening was carried out and compared with the results from the first screening in order to evaluate the effect of the suggested measures. At the same time an investigation of the cleaning efficiency was also carried out by monitoring the level of antibiotic substances directly before and after cleaning.

Material and methods

Material and chemicals

All chemicals were of analytical grade or higher quality and the water was purified in a Milli-Q water purifier (Millipore Corp., Billerica, MA, US). Twelve antibiotic substances were included in the screening. They are listed below with trivial name and the chemical names in brackets, all according to FASS [15]. The substances were: Cefadroxil [(6R,7R)-7-[(R)-2-Amino-2-(p-hydroxifenyl)acetamido]-3-metyl-8-oxo-5-tia-1-azabicyklo[4.2.0]okt-2-en-2-karboxylsyra], Cefalexin [(6R)-7R-7-[(R)-2-Amino-2-fenylacetamido]-3-metyl-8-oxo-5-tia-1-azabicyklo[4.2.0]okt-2-en-2-karboxylsyra], Ciprofloxacin [1-Cyklopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-kinolinkarboxylsyra], Demeclocyklin HCl [7-Chloro-4.(dimethylamino)-1,4,4a,5,5a,6.11,12a-octahydro-3,6,10.12.12a-pentahydroxy-1,11-dioxo-2-], Diaveridin [2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine 5-((3,4-dimethoxyphenyl)methyl)-4-pyrimidinediamine], Doxycyklin [(4S,4aR,5S,5aR,6R,12aS)-4-Dimetylamino-1,4,4a,5,5a,6,11,12a-oktahydro-3,5,10,12,12a-pentahydroxi-6-metyl-1,11-dioxo-2-naftacenkarboxamid], Enrofloxacin [1-Cyklopropyl-7-(4-etyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-kinolinkarboxylsyra], Fluconazol [2,4-Difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmetyl)bensylalkohol], Metronidazol [1-(2-Hydroxietyl)-2-metyl-5-nitroimidazol], Norfloxacin [1-Etyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-kinolinkarboxylsyra], Ofloxacin [9-Fluoro-2,3-dihydro-3-metyl-10-(4-metyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazin-6-karboxylsyra], Trimetoprim [2,4-Diamino-5-(3,4,5-trimetoxibensyl)pyrimidin]. As internal standards, the following isotope labelled antibiotics were used: Enrofloxacin-D5, Fluconazol-D4, Norfloxacin-D5. The concentration varied between the compounds, but was in the range of 1500-1800 ng/mL.

Powder free disposal vinyl gloves (Evercare, Selfatrade AB, Spånga, Sweden) were used when collecting the samples. Wet tissues (Apoliva, Apoteket AB, Stockholm, Sweden) were used for collection of wipe samples. A homemade plastic frame (outer size 14 x 14 cm and encompassing 10 x 10 cm = 100 cm^2) was used to get a reproducible size of the wipe samples from flat surfaces. Screw capped plastic tubes (Sarstedt, 15 mL, Nümbrecht, Germany) were used to store the wipe samples.

Instrumentation

For the analysis, a PerkinElmer (Norwalk, CT, USA), chromatographic system consisting of two micro-pumps (PerkinElmer series 200) and an auto-sampler (PerkinElmer series 200) was used. The HPLC was equipped with a YMC Hydrosphere C18 column (YMC, INC., Wilmington, NC, US) 150*4.6 mm id, 5 um. Acetonitrile in water with 0.1% of formic acid were used as HPLC-eluent, starting at 15% of acetonitrile for 2 minutes followed by a gradient to 70% after 9 minutes. The HPLC was coupled to a triple quadrupole mass spectrometer (API 2000 PE Biosystem, Foster City, CA, USA) equipped with an electrospray ion source (TurboIonSpray). The ion spray voltage was set to 5.5 kV (positive mode) and the drying gas was at 350 °C.

Sampling procedure

The sampling for the screening was then made according to a previously reported procedure [16-17]. Wipe samples were collected from suitable surfaces using the plastic frame for flat surfaces. The area of non-flat sampled surfaces was carefully measured after the wipe sample was taken. Powder free disposal gloves were used and changed between each sample. For each sample a wet tissue was used. The tissue was cut in two halves using a pair of scissors. One half of the tissue was used to collect the sample and the other half was used to clean the plastic frame after sampling. The previously validated wipe procedure was employed when taking the samples. After wiping the surface, the wet tissue was folded once more and then rolled and placed into a screw capped plastic test tube. The samples were then stored in freezer (-20 C^{o}) until analysis.

Analytical procedure

The samples were analysed according to a method described elsewhere [14]. In short, the samples were thawed and the tissue in each tube was compressed to the bottom. Then, 5 mL of ethanol and 100 µL of each internal standard solution were added and the samples were shaken for 60 min. Then, 1.5 mL of the solution was transferred to micro-vials and evaporated to almost to dryness in a Speed Vac Concentrator (Savant Instruments Inc., Farmingdale, USA). The samples were re-dissolved in 100 µl 5% methanol in water, transferred to HPLC vials after 30 minutes and analysed by HPLC-MS/MS.

Selection of sites for screening

For selection of suitable sites for this screening, an inquiry (see Appendix 1) was sent out to 64 wards at 42 hospitals in the northern half of Sweden to investigate which antibiotic drugs that regularly were used and also to identify sites that were prepared to participate in the screening. Of the 64 wards, 36 answered the inquiry of which 24 were prepared to participate and 12 declined. Of these 24 sites, three were not included in the screening in the end due to difficult travel logistics. The screening was, thus, carried out at 21 hospital wards (intensive care, haematology, surgery or general wards) in 16 different hospitals in Sweden. The hospitals ranged from University hospitals to minor regional hospitals. All hospitals were public.

Screening procedure

Each ward was visited during the screening. At the visit, before any samples were collected, the facilities, compounding systems, compounding procedures, administration routines as well as cleaning and waste handling routines etc, were recorded and documented. During this evaluation focus were particularly put on the compounding system used, the place for compounding, the cleaning procedure, the cleaning frequency, the presence of written instructions for compounding, the average number of daily compounded doses, the number of individuals that made drug compounding as well as their experience (no of years with compounding) and the drugs that actually were used at the time of the screening. This documentation was also verified with a nurse at each ward that normally carried out compounding and administration of antibiotic drugs (usually the nurse that was responsible for the drug room).

At each ward, approximately 10 samples were collected. The samples were taken frombenches used both for compounding and not for compounding, drug shelves, waste containers, sinks, and the floor in the drug room, and from the toilet seat and the floor in patient toilets and from other relevant locations at the wards (e.g., nurse office, coffee room etc.). All sampling was carried out from June to November 2008. Appendix 2 summarizes the sampling locations at each ward.

From the results, the mean and median values, range and number of samples above the detection limit and the number of sampling locations with identified substance, were calculated for each

substance. In the mean value calculation, all results below the analytical detection limit (ADL) were assigned (ND-not detected) to:

$$ND = \frac{ADL}{\sqrt{2}}$$

According to Hornung and Reed [18], this method to handle ND-values gives more adequate results than ND=ADL/2 when data has a log-normal distribution. This is normally the case with data series that has a lower limit but virtually no upper limit, like in this case.

Classification procedure

To get a reasonable overview and be able to compare the level of spill and leakage, the wards were classified into four categories. Each ward was given a score according to the results of the following parameters: i) the number of found substances (one point for each substance), ii) the number of samples with substances (one point for each substance in a sample) and iii) the level of the substances (for each substance 0.01-0.1 ng/cm^2=1 point; 0.1-0.5 ng/cm^2=2 points; 0.5-1.0 ng/cm^2=3 points; 1-2 ng/cm^2=4; 2-5 ng/cm^2=5; 5-10 ng/cm^2=6; >10 ng/cm^2=7). A high score, thus, meant a large spill and leakage. The range of points from the lowest to the highest score was divided into four ranges of equal numerical size, representing the four categories: *Low, Medium, High* and *Very high* level. Based on the individual score, each ward was then classified into one of the categories.

Evaluation of spatial distribution patterns

Based on the results for different sampling locations at each ward the spatial distribution patterns were evaluated. The results from primary surfaces, where antibiotics were handled, i.e., work benches for compounding drugs, drug shelves etc, and the results from secondary surfaces, where antibiotics not were handled, i.e., floors, benches not used for compounding etc, were considered. Based on the differences between the results from primary and secondary surfaces, various spatial distribution patterns were identified.

Effect of compounding system on the level of spill and leakage

Numerous studies on handling of cytostatics have shown that the compounding system have a significant impact on the level of drug spill and leakage [1]. In order to investigate the effect of the compounding system during preparation of antibiotic drugs, the compounding systems used at the wards were classified into three categories: i) open systems with a venting needle without filter or with the traditional "milking technique", ii) some type of spike with filter for venting (e.g., Mini-spike™, Braun Medical AB, Danderyd, Sweden or Venting-needle™, Baxter Medical AB, Kista, Sweden), and iii) closed compounding system (e.g., PhaSeal™, Carmel Pharma AB, Gothenburg, Sweden or Tevadaptor™, Teva Sweden AB, Helsingborg, Sweden). For each ward, the classification level of the ward was compared to the compounding system category used at the ward.

Selection of sites for the investigation of preventive measures

In the second part of this study, three wards, classified as having *Very high* contamination level, were selected. The compounding and administration procedures were recorded step by step in order to identify possible causes to the spill and leakage. Based on this documentation, a number of preventive measures to minimize spill and leakage, as well as measures to prevent the spatial distribution of emerged spill and leakage were suggested. Examples of suggested measures are presented in Appendix 3. The preventive measures were individually suggested to each ward based on their particular situation and presented to the staff in a written document. At each ward, the staff then decided by themselves, which of the suggested measures that should be implemented. About two month after the selected measures were introduced at the ward, a follow-up screening was carried. At the follow-up screening, wipe samples were collected on the same surfaces as in the first screening.

Assessment of the cleaning procedure

The cleaning procedure may have a significant impact on the level of spill and leakage of cytostatics [1,19-20]. During the second part of this project, a possibility to investigate the effect of the generally used cleaning procedure was possible. At the follow-up screening, samples were

also collected immediately before and after general cleaning of the work benches and floor in the drug rooms and on the floor in the patient toilets.

The general cleaning procedure was similar at all three wards. The floor was wiped with a mop, dampened in a water-detergent solution. The mop cloth was changed between each room and the used mop clothes were washed in a laundry, dried and reused, until worn out.

Results and discussions

Initial survey

Table 1 shows the antibiotic substances that were identified to be active compounds in the drugs that were specified by the wards in the survey to be regularly used. Twenty-five compounds were identified to be used in at least one drug at one of the wards. Two of the compounds determined in this screening (Cefalexin and Diaveridin) were not listed in the survey as regularly used. A limited number of compounds were present in frequently used drugs. Ciprofloxacin present in drugs used at all sites, and Cefuroxim, Fluconazol, Meropenem, Metronidazol and Trimetoprim were present in drugs used at more than 70 % of the screened sites. Eight of the compounds were present in drugs that were used in less than 15 % of the sites. Three compounds (Cefuroxim, Meropenem and Tazocin) were present in frequently used drugs but were not analysed in the screening. However, the four compounds (Ciprofloxacin, Fluconazol, Metronidazol and Trimetoprim) that were present in the most frequently used drugs were all included in the screening.

Screening

Twelve different antibiotic substances were analysed in 206 samples collected at 21 wards at 16 different hospitals. The results from the screening are summarized in Table 2.

Ciprofloxacin was the substance that occurred most frequently in the samples and was identified in samples from all wards. It was a substance that was specified in the survey to be present in drugs that were administered both as infusion and as tablets. Ciprofloxacin occurred in at least one sample at >10 ng/sample at all wards. Other substances that were present in amounts >10 ng/sample at many wards were Metronidazol (19 wards), Fluconazol (17 wards), Trimetoprim

(15 wards). All three of these substances occur in antibiotics administered both as infusion and tablets.

Metronidazol had the highest mean value of 2.4 ng/cm^2, the highest median value (0.061 ng/cm^2) as well as the second highest individual value (205 ng/cm^2). Trimetoprim showed the highest individual value, which was 340 ng/cm^2, and the second highest mean value (1.92 ng/cm^2). The second highest median value was 0.022 ng/cm^2 and was obtained for Doxycyklin. Diaveridin was the substance that showed both the lowest mean and median values, which were 0.002 ng/cm^2 and < 0.001 ng/cm^2, respectively.

It is also worth to note that the substances that were specified in the survey to only be present in drugs administered as tablets (Cefadroxil, Cefalexcin, Enrofloxacin, Norfloxacin och Ofloxacin) also could be identified in several samples. At least one of these substances was present at a level > 10 ng/sample at eleven wards. The levels of these substances, however, were generally lower compared with substances present in drugs that were administered by infusion too. This means that handling tablets, e.g., splitting tablets, filling tablet dispensers (a box with compartments for several doses, usually for one week), also caused distribution of drug particles. It is, thus, also necessary to consider handling tablets to efficiently reduce spill and leakage of antibiotics.

Both Cefalexcin and Diaveridin were discovered in several samples, although no ward had specified that drugs, containing these substances were used. One reason to the occurrence of these substances could be that the staff was unaware of that such drugs were used or that such drugs had been used before or after the time of the survey.

Classification of the wards

To be able to get an overview of all data and to compare the wards, a classification system was designed. Three basic parameters were considered in the classification: i) the number of substances found, ii) the number of contaminated locations and iii) the level of the spill. The classification levels are relative to the range from the lowest to the highest score for each parameter. The reason for a relative scale was that there was no information on which level of spill is to be expected. With a relative scale, additional data can be added in the future to adjust the scale.

Table 3 shows the classification of the wards that participated in the screening. Of the 21 wards, four were classified as *Low*, six as *Medium*, eight as *High* and, finally, three as *Very high*. This means that 11 of the 21 wards (52 %) were classified as *High* or *Very high*.

At the wards with the highest classification level, at least one substance was found in all samples. A total of nine different substances were found of which three substances occurred at levels > 5 ng/cm^2. This indicates a significant spill and leakage at these wards with a significant distribution to secondary surfaces.

At the wards with the lowest classification, substances were found in, at the most, 1-4 samples. Not more than two to four substances were found, all at levels below 0.5 ng/cm^2 and most substances < 0.1 ng/cm^2. This result shows that it is possible to handle antibiotics with only insignificant spill and leakage. The screening, however, showed that only 14 % of the wards (3 of 21) manage to handle antibiotics in that way.

Spatial distribution patterns

Based on the data from all sampling location at all wards, considering the distribution from primary surfaces towards secondary surfaces, three different distribution patterns could be perceived.

Pattern 1: Small spill and leakage occurred on primary surfaces at the compounding place like work bench and waste container. There was no or only insignificant distribution to secondary surfaces like benches where no drugs were handled or to the floor in the drug room or to other rooms. This pattern indicates that the way of working is well adapted for the purpose. Only limited spill and leakage occur. The routines for cleaning are also suitable and prevent that emerging spill and leakage will be distributed to secondary surfaces.

Pattern 2: Larger spill and leakage can be shown on primary surfaces at the compounding place such as work bench and waste container but also a significant distribution to secondary surfaces occur, e.g., to adjacent benches, where no drugs are handled, or to the floor. Drugs can usually also be found in patient toilets and wash rooms. This pattern indicates that spill and leakage frequently occur. Moreover, the routines for cleaning are not fully sufficient to prevent that spill and leakage are distributed to secondary surfaces.

Pattern 3: Large spill and leakage occur and are distributed on to both primary and secondary surfaces. Frequently, there are larger levels of contamination on the secondary surfaces such as the floor, the sink in wash rooms and patient toilets. The occurrence of this distribution pattern indicates that the way of working regularly results in spill and leakage. Furthermore, the result shows that the routines for cleaning are not sufficient to prevent that the spill and leakage is significantly distributed to secondary surfaces.

All the wards that had been classified as *Low* showed distribution pattern 1. The wards that had been classified as *Very high*, all showed distribution pattern 3, as well as most of the wards that had been classified as *High*. A majority of the wards that had been classified as *Medium* showed distribution pattern 2.

Effect of the compounding system

Many antibiotics aimed for infusion are sold as dry substance in glass vials sealed with an aluminum cap and a rubber stopper. For illustration, a short description of how an infusion bag can be prepared and at which operations spill and leakage can be expected to emerge is given below.

When compounding antibiotics for infusion, a disposal syringe is filled with a suitable aliquot of saline solution from a storage bottle. The syringe is fitted with an injection needle and the liquid is injected into the vial through the rubber stopper. To eliminate the increased pressure that builds up during the injection the traditional "milking technique" or some kind of venting system are used, e.g., an extra open injection needle, a filter spike (e.g. Braun Mini-spike™ or Baxter Venting-needle™) or a closed system (e.g. PhaSeal™ or Tevadaptor™). During this operation, dry substance or liquid may be expelled to the air as aerosol depending on how efficient the venting system can collect the formed aerosol. The dry substance is then dissolved in the vial and the desired volume of the dissolved drug is drawn back into the syringe. Then, the syringe is disconnected from the drug vial. Liquid spill or aerosol emission can occur at this operation. The syringe is then connected to an inlet port of the infusion system and the drug is injected into the infusion liquid. In some occasions, the syringe is disconnected from the inlet port after injection and in other occasions, the syringe is left connected to the inlet port. In the first case, spill or aerosol emission can occur when the syringe is disconnected. Other operations when spill or aerosol emission can

occur are when the tubing in the infusion system is filled, when drug infusion bag is connected to or disconnected from the infusion system.

Of the wards participating in the screening, four stated that they used some kind of closed system (e.g. PhaSeal™ or Tevadaptor™) for compounding antibiotics for infusion. Three wards stated that they regularly used only an extra open injection needle for venting the vials or ”milking” technique. The other 14 wards used some kind of injection needle with filter or spike (e.g. Braun Mini-spike™ or Baxter Venting-needle™) for venting the vials.

A comparison of the classification results and the compounding system used at the wards showed a clear correlation. Figure 1 shows the result of this comparison. All four wards that used closed systems were among the six wards that had the lowest spill and leakage, i.e. classification *Low* or *Medium*. Correspondingly, all three wards that used “milking technique” or an open injection needle for venting were among the six wards with the highest contamination level in the screening, i.e. classification *High* or *Very high*.

Description of preventive measures

Three wards, with classification *Very high,* were selected for the extended investigation to study the effect of preventive measures. All three wards were visited twice during the extended study. At the first visit, the compounding work was studied operation for operation and the whole compounding procedure was documented. At a second visit a follow-up screening was carried out.

After examination of the compounding procedures a range of measures to prevent spill and leakage as well as the distribution of any emerging spill were documented. Below are examples of preventive measures that were suggested (see also Appendix 3).

Measures to minimize spill and leakage during compounding

Consider using a closed system for compounding antibiotics. Studies of cytostatics [1] have shown that using closed compounding systems can contribute to significantly reduce the spill and leakage.

When filling tubings in infusion systems, collect any emerging liquid from the tubing nozzle over a bench cover with plastic bottom or a collection container. Do not hold the tubing nozzle so any spill land on the floor or bench top.

When using infusion bags pre-filled with antibiotics, fill the tubings of the infusion system first with saline solution to evacuate air instead of using the drug solution and administer saline solution after infusion is completed to evacuate any remaining drug solution before disconnecting the infusion system from the patient. With this procedure, any emerging spill during these operations will contain only saline solution and minimize the risk for drug spill.

When handling tablets, e.g., splitting tablets and filling drug dispensers, use disposal gloves and carry out these operations on a bench cover with plastic bottom to collect any emerging drug dust. Discard the cover and gloves after the operations are finished.

Prepare infusion systems as much as possible in the drug room. This minimize the risk for spill and leakage in the ward rooms.

Measures to minimize distribution of emerging spill and leakage

Use disposal gloves when doing compounding and change gloves between each compounding. This prevents skin exposure but also to prevent that any spill on the gloves are distributed from one compounded infusion bag to the next.

Carry out compounding on a bench cover with plastic bottom that is discarded after each compounding. Any emerging spill will then be collected on the cover and this minimize the risk that the spill becomes distributed to other surfaces.

Change disposal gloves when leaving the drug room with the prepared drug. This minimize the risk to distribute drugs from contaminated gloves.

Any visible spill on benches, floor or other surfaces should immediately be wiped and the surface should then be cleaned with water and detergent before any disinfection with 70 % alcohol. Alternatively, use a cleaning alcohol solution, e.g., 45 % alcohol in water with a tenside (e.g., M-Ytdes 45+®, Kemetyl, Stockholm). Drug spill that is allowed to dry will be more difficult to clean [1].

Always clean benches and other surfaces with water and detergent before any disinfection with 70% alcohol solution. Alternatively, use a cleaning alcohol solution (e.g., M-Ytdes 45+®). Drug contaminations are generally more soluble in water than alcohol and will be easier to wash away with water [1]. If a cleaning alcohol solution is used on a daily basis for general cleaning, a thin film of tenside will be formed. It is therefore recommended to clean the surfaces with water on regular bases to remove this film, e.g., once a week.

Another parameter to reduce the distribution of spill and leakage is an efficient and well-adapted general cleaning procedure. Studies have shown that there are significant difficulties to wash away drug spill and leakage [1, 19-20]. If spill are taken care of immediately, it is much easier to wash away. If the spill has been allowed to dry, it is much more difficult to clean [1].

Patients under treatment usually excrete significant amounts of drugs and drug contaminated surfaces are often found in patient areas. Particularly patient toilets have been shown to be highly contaminated [19].

When cleaning the floor in areas where drug spill can be expected, it is recommended to mop the floor two times with a change of mop cloth in between to improve the result and contribute to decrease the distribution of emerged spill.

Currently, cleaning within medical care in Sweden is much focused on aseptic procedures to prevent growth and distribution of bacteria and other germs [1]. Good information on how to wash away drug spill is, however, often lacking. It is essential that the cleaning staff gets correct information and education to carry out an adequate cleaning.

Benefits of preventive measures

To evaluate the effect of the suggested measures, three wards were invited to participate in a limited study. At each ward, the staff got a list of suggested measures and decided among themselves which of the suggested measures they should implement. About two month after the implementation of the selected measures, a follow-up screening was carried out. At this screening wipe samples were collected at the same locations as in the first screening. The results from this follow-up screening are reported in Tables 4 to 6.

Hospital 1, Surgery ward, was classified as *High*, which was a reduction from *Very high* in the first screening. There was at least one antibiotic substance in all samples (see Table 4). Ten different substances were found compared with seven at the first screening, which resulted in the classification level *High*. The levels of the substances were considerably lower than in the first screening. In the majority of the samples, the levels were < 0.1 ng/cm^2. Only Metronidazol was found at levels > 0.5 ng/cm^2 in two samples.

An improvement was also obtained at Hospital 14, Hematology ward. In nine of ten samples, there was at least one substance, which can be seen in Table 5. Only four substances were found compared with six in the first screening. None of the substances were present in levels > 0.5 ng/cm^2 in any of the samples. This resulted in a change of classification level from *Very high* to *Medium* in the follow-up screening.

Twelve of the samples at Hospital 15, General ward, showed presence of antibiotic substances at the follow-up screening (see Table 6). Nine different substances were found compared with six in the first screening. A majority of the samples showed levels < 0.1 ng/cm^2. The levels were consequently considerably lower than at the first screening. The ward was, however, classified as *High*, compared with *Very high* at the first screening. The major reason for this was the large number of substances present.

The results from the follow-up screening (see Tables 4-6) show for all three wards that there were lower amounts of antibiotic substances in the samples compared with the first screening. It were mainly on the surfaces that had high levels in the first screening that showed lower levels in the follow-up screening and this was valid for both primary and secondary surfaces. This means that the spill and leakage that occur had decreased. At the follow-up screening, the wards had implemented several of the suggested measures for two month. At all three wards, disposal gloves were used and changed after each compounding. The compounding was carried out on a bench cover, with plastic bottom, that was changed after each compounding. The bench top surfaces were cleaned and disinfected with cleaning alcohol solution (M-Ytdes45+®) instead of 70% alcohol. None of the wards had changed to a closed compounding system. Two of the wards had changed from open venting system to a filter spike for venting.

The suggested and implemented measures have given some effect in reducing the spill and leakage as well as the distribution of emerging spill and leakage. Rather simple measures can contribute to decrease the spill and leakage that occur during compounding and other handling of antibiotic drugs. The first screening showed that it is possible to make compounding with almost no spill and leakage, i.e., by employing closed systems. One important outcome of this study has been an emerging awareness of the problem with spill and leakage and an ongoing discussion at the wards on how to improve the compounding procedures to reduce drug spill and leakage.

During the visits at the wards during the follow-up screening, the staff showed an awareness that spill and leakage could occur and cause problems. This awareness contributed to a more concerned attitude, which influenced the individuals' method of working in a positive direction.

Cleaning efficiency

An investigation the cleaning efficiency was also carried out during the follow-up screening. Wipe samples were collected from various surfaces immediately before and after normal cleaning in drug rooms and patient toilets. All three wards had, according to the suggested measures, implemented cleaning of the benches with cleaning alcohol solution (M-Ytdes45+®) and compounding on bench covers with plastic bottom. They also used a filter-spike for venting drug vials during compounding. None of the wards had, however, implemented a closed system for compounding. In all cases, the floors in the drug rooms and patient toilets were cleaned once every weekday with a humidified mop, where the mop cloth was changed for each room. The used mop cloths were washed in a laundry and reused until worn out. The recommended double mopping had not been implemented at any ward. Nor had an increased cleaning frequency been implemented. According to the current handbook for hospital care [21], all medical staff are expected to clean visible spill and leakage in between regular cleaning occasions. The result from this investigation is presented in Table 7.

At Hospital 1, Surgery ward, a comparison of the contamination on the floor in the drug room before and after cleaning was carried out. Five different substances were found in the samples. The result shows that the same amounts of the substances were found after as found before the cleaning.

The comparison at Hospital 14, Hematology ward, comprised floors in the drug room and a patient toilet as well as two benches in the drug room used for compounding. On the floor in the drug room four substances were found and two or three substances on other surfaces. The result shows that there are substances remaining on the surfaces after cleaning. On the benches about 50 – 70 % of the original concentration of the substances was left after cleaning. On the floor in the patient toilet, it was the same level of substances before and after cleaning and about 50 % of the original concentration of the substances was left on the floor in the drug room after cleaning.

At Hospital 15, General ward, wipe samples were collected at two places on the floor in the drug room and on the floor in one patient toilet. Wipe samples were also collected before and after cleaning on benched for compounding both on a surface that was clean with water, on a surface cleaned with cleaning alcohol solution (M-Ytdes45+®). After the floor cleaning, some substances were absent, e.g., Ciprofloxacin, while others were found, e.g., Cefalexin. The levels of the substances decreased slightly for some substances, e.g., Diaveridin and Metronidazol. At the same time, the level also increased after the floor cleaning for other substances, e.g., Trimetoprim. The cleaning of the benches gave a more uncertain result. Only two substances were found before cleaning, while after water cleaning, five substances were found, and after cleaning with a cleaning alcohol solution (M-Ytdes45+®), five substances were found.

At this investigation wipe samples were collected at two adjacent surfaces before and after cleaning. If there had been small very local spill it could have been present on only one of the surfaces. This may explain why, occasionally, a substance could be found in one sample but not the other.

This investigation shows that the cleaning methods used need to be improved to efficiently remove spill and leakage of antibiotics. Cleaning bench surfaces with water or cleaning alcohol solution (45%) with a tenside gave similar result but did not manage to completely remove spill and leakage. Wiping the surfaces two times and changing the wipe tissue in between might improve the result.

The floor cleaning gave poor result why it is particularly important to improve the floor cleaning methods. Doubled mopping of the floor with change of mop cloth may improve the cleaning result. Doubled mopping was, however, not used at these occasions, since none of the wards had implemented that as normal cleaning procedure. Today a humidified mop is used. To improve the solubility of the drugs it might be necessary to use more water when cleaning floors where drug contamination can occur.

These simple measures may improve the cleaning result. The cleaning methods at Swedish hospitals are similar and it could be advisable to carry out a coordinated study to develop suitable cleaning methods to efficiently remove spill and leakage of antibiotics.

Occupational hygiene aspects

The result from this study shows that spill and leakage of antibiotics normally occur in not insignificant amounts. The screening, however, also showed that it is possible to handle antibiotics in medical care with only very small spill and leakage, particularly when closed systems were employed (e.g., PhaSeal™ or Tevadaptor™).

The Swedish Work Health Authority Ordinance on Handling Cytostatics and other drugs with persistent toxic effects [5] also cover several antibiotic drugs, e.g. Penicillins, Cephalosporins and some β-lactams. This ordinance comprise regulations on how these drugs should be handled during compounding and administration. It also covers waste handling and requirements for proper training and technical facilities.

Cefadroxil and Cefalexin are cephalosporins that were analyzed in this study. The result also shows that spill and leakage of these substances occur.

According to the Ordinance [5], these drugs should be handled in such way that the staff do not become occupational exposed. Moreover, the technical systems used for compounding and administration should be tested for leakage in every day work on a regular basis. Also, waste handling shall be organized in such way that spill and leakage is minimized so no exposure occur. The staff shall also get adequate education to be able to handle the drugs in a safe way.

Consequently, it is, from occupational hygiene viewpoint, important to more systematically control spill and leakage of antibiotics in every day work. If such controls show that spill and leakage occur and that the staff becomes exposed, implementation of closed handling systems ought to be considered, especially for those drug types listed in the Ordinance [5].

Conclusions

The method used in this study is efficient and rapidly gives an extended picture of the spill and leakage that occur. With simultaneous determination of twelve different antibiotic substances that are active component in frequently used antibiotics today, the method gives a good view over the distribution of spill and leakage in most situations where antibiotics are handled.

The screening showed that spill and leakage of antibiotics occur. At least one substance in at least one sample was found at all wards that participated in the screening. The substances that were found in highest levels, all were active substances in drugs frequently administered both as tablets and as infusion. However, substances that were active substance in drugs only administered as tablets were also found. This means that also handling tablets must be considered when assessing spill and leakage of antibiotics as well as the staff exposure risks.

The wards that participated in the screening were classified into four groups depending on the contamination level. In this classification the following parameters were considered: i) the number of substances found; ii) the number of samples with substances; and iii) the level of contamination. Three of the 21 wards were classified as *Very high*, eight as *High*, six as *Medium* and four as *Low*.

Different compounding systems affect the proportions of the spill and leakage. Employing a closed system will efficiently reduce the spill and leakage, while the use of a venting system without any filter gives large spill and leakage. The three wards that regularly used closed systems were all among the five wards with the lowest contamination level. In the same time, all three wards that used open venting systems, all were among the five wards with the highest contamination level.

Simple measures, such as using disposal gloves and bench covers and change these between each compounding and cleaning benches and other surfaces with cleaning alcohol (45%) with tenside instead of 70% alcohol, all contribute to reduce the spill and leakage that occur as well as the distribution of the emerging spill and leakage. At all wards that participated in the follow-up screening, the contamination levels with antibiotics had decreased after implementation of preventive measures. The first screening, however, showed that it is possible to obtain almost insignificant contamination levels. It is, consequently, important to discuss how to find adequate and safe procedures for handling antibiotics to minimize the spill and leakage, e.g., by employing closed systems.

Measurements before and after cleaning showed that only minor part of the contamination were removed with the regular cleaning procedures used today. It is therefore important to improve the cleaning methods. The cleaning methods at Swedish hospitals are similar. It can, thus, be appropriate to carry out a coordinated investigation to improve the cleaning methods to remove drug contamination on various surfaces.

Several of the substances, found in the screening, are covered by the Swedish Work Health Authority Ordinance [5]. According to the Ordinance handling of these drugs should be in such way that the staff does not become exposed to these drugs. Moreover, the handling systems used shall be controlled for spill and leakage in every day work. From occupational hygiene point of view, a more systematic control of spill and leakage is recommended. If such controls show that spill and leakage occur, implementation of closed system ought to be considered.

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Table 1. *Antibiotic substances used in drugs that are regularly used at the wards according to the survey.*

The compounds in bold have been determined in this screening. Substance trivial names are given according to FASS [15].

Hospital no / ward	Amoxicillin	Benzylpenicillin	**Cefadroxil**	**Cefalexin**	Cefotaxim	Ceftadizim	Cefuroxim	**Ciprofloxacin**	Clindamycin	Cloaxillin	**Demeclocyklin HCl**	**Diaveridin**	**Doxycyklin**	**Enrofloxacin**	Flucloaxillin	**Fluconazol**	Gentamicin	Imipenem	Meropenem	**Metronidazol**	**Norfloxacin**	**Ofloxacin**	Pivmecillinam	Tazocin	Tobramycin	**Trimetoprim**	Vancomycin
1 / Intensive care							X	X			X		X			X		X	X	X	X	X				X	
1 / Surgery			X				X	X		X			X			X				X		X				X	
2 / Hematology						X		X			X		X			X					X	X		X		X	
2 / Infection		X						X	X	X						X	X		X	X				X		X	
3 / Intensive care					X		X	X		X			X			X		X	X	X						X	
4 / Surgery							X	X	X				X						X	X	X	X		X			
5 / Hematology			X			X	X	X			X		X			X		X	X		X	X		X		X	
6 / Hematology-Oncology		X	X				X	X					X	X		X			X	X	X	X		X		X	
7 / Infection		X	X		X		X	X		X										X		X		X			
7 / Hematology	X		X		X		X	X			X		X		X	X			X	X	X	X				X	X
8 / General ward	X	X	X				X	X			X		X			X				X			X			X	
9 / Infection		X					X	X		X	X		X	X		X				X	X	X		X	X		
9 / Hematology		X					X	X	X		X		X			X			X	X	X	X		X		X	X
10 / Infection					X		X	X	X	X						X				X							X
11 / Infection		X			X		X	X		X								X		X							
12 / Surgery			X				X	X	X										X	X				X			
13 / General ward		X			X			X							X		X		X	X				X		X	
14 / Hematology			X					X			X		X			X				X	X	X				X	
14 / Infection		X					X	X	X	X			X			X				X	X			X		X	
15 / General ward			X		X			X		X						X			X	X	X			X		X	
16 / General ward					X		X	X		X						X				X						X	

Table 2. *Results of the screening.*

A total of 206 samples collected from 21 wards at 16 different hospitals. DL – detection limit; QL – quantification limit (10 x DL). Substance trivial name according to FASS [15].

Compound	Mean	Median	Range (min – max)	No of samples	No of samples	No of wards	Comments
	ng/cm^2	ng/cm^2	ng/cm^2	above DL	above QL	above DL	
Cefadroxil	0,028	0,006	< 0,001 – 0,595	161	73	19	
Cefalexin	0,006	0,004	< 0,001 – 0,070	152	49	19	2nd lowest mean and median
Ciprofloxacin	1,702	0,048	< 0,001 – 312,6	203	161	20	2nd highest mean and median, most samples above QL
Demeclocyklin HCl	0,037	0,013	< 0,001 – 1,019	199	116	20	
Diaveridin	0,002	< 0,001	< 0,001 – 0,077	163	8	18	Lowest mean and median
Doxycyklin	0,073	0,022	< 0,001 – 0,900	204	129	20	Most frequently occuring compound
Enrofloxacin	0,015	0,007	< 0,001 – 0,152	192	80	19	
Fluconazol	0,581	0,009	< 0,001 – 76,06	202	100	19	
Metronidazol	2,407	0,061	< 0,001 – 205,2	202	154	20	Highest mean and median, 2nd highest concentration
Norfloxacin	0,041	0,016	< 0,001 – 0,550	178	118	19	
Ofloxacin	0,031	0,011	< 0,001 – 0,797	202	107	19	
Trimetoprim	1,927	0,007	< 0,001 – 339,6	181	94	20	Highest concentration

Table 3. *Classification of the contamination level at the wards that participated in the screening.*

Class levels are: Low (-), Medium (0), High (+) and Very high (++). The classification criteria are described in the text.

Hospital	Ward	Class
1	Intensive care	+
1	Surgery	++
2	Hematology	+
2	Infection	+
3	Surgery	0
4	Intensive care	0
5	Hematology	0
6	Hematology/oncology	+
7	Infection	-
7	Hematology	+
8	General care	+
9	Infection	0
9	Hematology	+
10	Infection	0
11	Infection	-
12	Surgery	-
13	General care	-
14	Hematology	++
14	Infection	0
15	General care	++
16	General care	+

Table 4. *Result from the follow-up screening at Hospital 1, Surgery ward. Substance trivial names according to FASS [15].*

Substance	Place	Level (ng/cm^2)						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10,0	> 10,0
Cefadroxil	Drug room, floor, below compounding bench, after cleaning	X						
Ciprofloxacin	Drug room, sink at compounding bench, in stainless steel	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						
Demeclocyklin HCl	Drug room, compounding bench in stainless steel	X						
	Drug room, work bench, below drug shelves	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Wash room, sink for urine measurements, "dirty"side	X						
	Drug room, work bench, below drug shelves	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, drug shelf (trimetoprim)	X						
Flukonazol	Drug room, work bench, below drug shelves	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
Metronidazol	Drug room, work bench, below drug shelves		X					
	Drug room, floor, below compounding bench, before cleaning			X				
	Wash room, floor, below waste box		X					
	Wash room, floor, below clean side of sink	X						
	Drug room, floor, below compounding bench, after cleaning			X				
	Patient toilet, floor, below toilet, after cleaning		X					
Norfloxacin	Drug room, compounding bench in stainless steel	X						
Ofloxacin	Drug room, compounding bench in stainless steel	X						

Table 4. *Continued…*

Substance	Place	Level (ng/cm^2)						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10,0	> 10,0
Trimetoprim	Drug room, compounding bench in stainless steel		X					
	Drug room, work bench, below drug shelves	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, drug shelf (trimetoprim)		X					
	Drug room, floor, below compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						

Table 5. *Result from the follow-up screening at Hospital 14, Hematology ward. Substance trivial names according to FASS [15].*

Substance	**Place**	**Level (ng/cm^2)**						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10	> 10
Cefadroxil	Patient toilet, floor, below toilet, after cleaning	X						
Flukonazol	Drug room, compounding bench to the right, before cleaning	X						
	Drug room, floor, below compounding bench, before cleaning		X					
	Drug room, compounding bench to the right, after cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, before cleaning		X					
	Patient toilet, floor, below toilet, after cleaning		X					
Metronidazol	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, drug shelf (Metronidazol)	X						
	Drug room, floor, below compounding bench, after cleaning	X						
Trimethoprim	Drug room, compounding bench to the left, before cleaning	X						
	Drug room, compounding bench to the right, before cleaning	X						
	Drug room, floor, below compounding bench, before cleaning		X					
	Drug room, drug shelf (Metronidazol)	X						
	Drug room, compounding bench to the right, after cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, before cleaning		X					
	Patient toilet, floor, below toilet, after cleaning		X					

Table 6. *Result from follow-up screening at Hospital 15, General ward. Substance trivial names according to FASS [15].*

Substance	Place	Level (ng/cm^2)						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10	>10
Cefadroxil	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, drug shelf (Trimetoprim)	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Drug room, floor, below bench beside compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, before cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						
	Drug room, compounding bench, after cleaning with M-Ytdes45+®	X						
	Drug room, compounding bench, after cleaning with water	X						
	Drug room, bench beside compounding bench, after cleaning with M-Ytdes45+®	X						
Cefalexin	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, drug shelf (Trimetoprim)	X						
	Drug room, floor, below compounding bench, after cleaning		X					
	Drug room, floor, below bench beside compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						
	Drug room, compounding bench, after cleaning with water	X						
Demeclocycline HCL	Drug room, bench beside compounding bench, before cleaning	X						
	Drug room, sink, before cleaning	X						
	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, drug shelf (Trimetoprim)	X						
	Drug room, floor, below compounding bench, after cleaning	X						

Table 6. *Continued …*

Substance	Place	Level (ng/cm^2)						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10	>10
Diaveridine	Drug room, bench beside compounding bench, before cleaning	X						
	Drug room, sink, before cleaning	X						
	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, drug shelf (Trimetoprim)	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Drug room, floor, below bench beside compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						
	Drug room, compounding bench, after cleaning with M-Ytdes45+®	X						
	Drug room, compounding bench, after cleaning with water	X						
Doxycycline	Drug room, bench beside compounding bench, before claning	X						
	Drug room, sink, before cleaning	X						
	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, floor, below bench beside compounding bench, after cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
Fluconazol	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Patient toilet, floor, below toilet, before cleaning	X						
	Drug room, compounding bench, after cleaning with M-Ytdes45+®	X						
	Drug room, compounding bench, after cleaning with water	X						
	Drug room, bench beside compounding bench, after cleaning with M-Ytdes45+®	X						

Table 6. *Continued …*

Substance	Place	Level (ng/cm^2)						
		0,01-0,1	0,1-0,5	0,5-1,0	1,0-2,0	2,0-5,0	5,0-10	>10
Metronidazol	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Patient toilet, floor, below toilet, before cleaning		X					
	Drug room, waste container	X						
	Drug room, compounding bench, after cleaning with M-Ytdes45+™		X					
	Drug room, compounding bench, after cleaning with water		X					
Ofloxacin	Drug room, bench beside compounding bench, before cleaning	X						
	Drug room, sink, before cleaning	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, floor, below compounding bench, after cleaning	X						
Trimethoprim	Drug room, compounding bench, before cleaning	X						
	Drug room, bench beside compounding bench, before cleaning	X						
	Drug room, sink, before cleaning	X						
	Drug room, floor, below compounding bench, before cleaning	X						
	Drug room, floor, below bench beside compounding bench, before cleaning	X						
	Drug room, drug shelf (Trimetoprim)	X						
	Drug room, floor, below compounding bench, after cleaning	X						
	Drug room, bench beside compounding bench, after cleaning		X					
	Patient toilet, floor, below toilet, before cleaning	X						
	Patient toilet, floor, below toilet, after cleaning	X						
	Drug room, compounding bench, after cleaning with M-Ytdes45+™	X						
	Drug room, compounding bench, after cleaning with water	X						

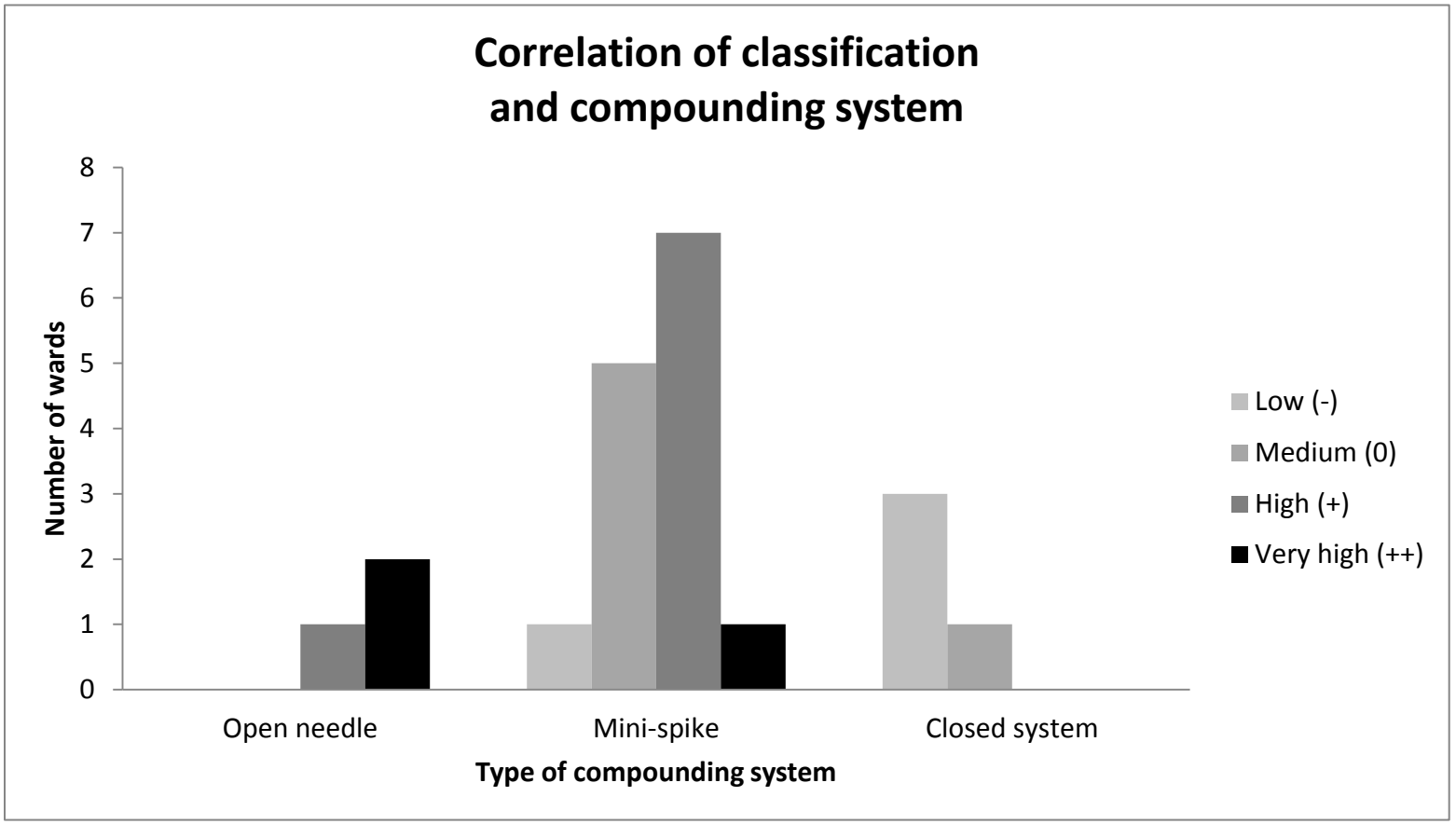
Table 7. *Result from the cleaning efficiency investigation.*

Substance trivial names according to FASS [15]. Samples collected before and after cleaning with W – water or M – M-Ytdes45+™, ND – not detected.

Antibiotic substance	Hospital 1, Surgery ward		Hospital 14, Hematology ward								Hospital 15, General ward								
	Drug room, floor		Drug room, floor		Left compounding bench		Right compounding bench		Patient toilet, floor		Drug room, floor 1st pos		Drug room, floor 2nd pos		Patient toilet, floor		Compounding bench		
	Before	After M	Before	After M	Before	After M	Before	After M	Before	After M	Before	After M	Before	After M	Before	After M	Before	After w	After M
Cefalexin	ND	ND	0,03	0,03	0,03	0,026	0,03	0,03	0,03	0,04	ND	0,14	0,09	0,04	ND	0,01	ND	0,02	ND
Ciprofloxacin	0,01	0,01	ND	ND	ND	ND	ND	ND	ND	ND	0,04	ND	0,03	0,02	0,11	ND	ND	0,19	0,10
Diaveridin	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0,01	0,05	0,08	0,02	0,01	0,02	0,02	0,01	0,01
Enrofloxacin	0,02	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Flukonazol	0,06	0,06	0,16	0,06	ND	ND	0,05	0,01	0,24	0,22	ND	ND	ND	ND	ND	ND	ND	ND	ND
Metronidazol	0,77	0,82	0,05	0,01	ND	ND	ND	ND	ND	ND	ND	ND	0,01	ND	0,19	ND	ND	0,12	0,20
Norfloxacin	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0,03	0,02	0,02	0,01	ND	ND	ND	ND	ND
Trimetoprim	0,07	0,10	0,10	0,05	0,02	0,01	0,07	0,05	0,21	0,32	0,06	0,08	0,08	0,11	0,01	0,02	0,08	0,04	0,02

Figures

Figure 1. *Correlation of classification of wards and the type of compounding system used for antibiotics. The classification levels (Low, Medium, High och Very high) are described in the text.*



Appendix 1.
(**Translated from Swedish)**

Introductory survey for the project:

Investigation of spill, leakage and staff exposure during handling of anitbiotics in hospital care

Running no X

1. We will participate in the project (circle appropriate)

   Yes, will participate No, will not participate

2. Unit (Hosptital and ward)

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3. Contact person (name, telephone, e-mail)

---

4. No of beds at the unit

---

5. No of staff that handles antibiotics

---

6. No of staff that nurse antibiotic treated patients

7. Totalt no of staff at the unit

8. How are antibiotics handled? (Circle correct (Yes or No) for each alternative)

a. We compound all antibiotics for infusion at the ward	Yes	No
b. We get all antibiotics from central compounding (e.g., pharmacy)	Yes	No
c. We both compound ourselves and get from central compounding	Yes	No
d. We compound antibiotics for bolus injections	Yes	No
e. We get prepared syringes for bolus inj from central compounding	Yes	No
f. We split tablets	Yes	No

9. List the five most frequently handled antibiotics and estimate the volumes (e.g., no of doses/week). Please also state the administration routes for each drug

Please fill in this form and return it in the added prepaid envelope.

Thank you for your participation

Appendix 2

Description of all sampling locations and all wiped surfaces at each ward.

BSC – Biological Safety Cabinet; Frame - a home made plastic frame encompassing 100 cm^2 (for details see section "Material and methods")

Hospital no / Ward	Sample location	Wiped surface
1 / Intensive care	Drug room, inner bench, left side	frame 10x10 cm
	Drug room, inner bench, middle	frame 10x10 cm
	Drug room, outer bench, left side	frame 10x10 cm
	Drug room, outer bench, right side	frame 10x10 cm
	Drug room, floor below outer bench	frame 10x10 cm
	Drug room, drug shelf above outer bench	frame 10x10 cm
	Cleaning room, sink at "dirty" side of bowl	frame 10x10 cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Cleaning room, drug waste container	Lid and handle 30x40 cm
	Surveillance room, floor by door to drug room	frame 10x10 cm
1 / Surgery	Drug room, sink for preparation, side of bowl	frame 10x10 cm
	Drug room, sink for preparation, bottom of bowl	Whole bottom 20x40 cm
	Drug room, work bench below drug shelf	frame 10x10 cm
	Drug room, floor below sink for preparation	frame 10x10 cm
	Cleaning room, sink for measuring urine volume at "dirty" side of bowl	frame 10x10 cm
	Cleaning room, drug waste container	Lid and handle 30x40 cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, hand basin	Whole bowl 40x30 cm
	Patient WC, floor below toilet	frame 10x10 cm

2 / Hematology	Drug room, BSC inside middle	frame 10x10 cm
	Drug room, shelf for drugs	frame 10x10 cm
	Drug room, drug waste container	Lid and handle 30x40 cm
	Drug room, floor below BSC	frame 10x10 cm
	Patient ward, drug waste container	Lid and handle 30x40 cm
	Cleaning room, sink at “dirty” side of bowl	frame 10x10 cm
	Cleaning room, drug waste container	Lid and handle 30x40 cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Patient WC, floor below toilet	frame 10x10 cm
	Patient WC, toilet	Seat ring 10x60 cm
2 / Infection	Drug room, laminar flow bench 1, middle	frame 10x10 cm
	Drug room, laminar flow bench 2, middle	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, needle waste box	Lid10 x 10 cm
	Drug room, drug waste container	Lid and lid handle 30x40 cm
	Drug room, floor below laminar flow benches	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, floor below toilet	frame 10x10 cm
	Cleaning room, sink front of needle waste box	frame 10x10 cm
	Cleaning room, floor below sink with needle waste box	frame 10x10 cm
3 / Intensive care	Drug room, preparation bench	frame 10x10 cm
	Drug room, sink side of bowl	frame 10x10 cm
	Drug room, floor below preparation bench	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, drug waste container	Top brim including folded bag 110x4 cm
	Cleaning room, sink opposite to drug waste container, side of bowl	frame 10x10 cm
	Cleaning room, drug waste containers	Top brim of two containers including folded bag 140x5 cm + 140x3 cm
	Cleaning room, floor below drug waste containers	frame 10x10 cm
	Cleaning room, shelf beside drug waste containers	frame 10x10 cm
	Coffee room / Office, floor	frame 10x10 cm

4 / Surgery	Drug room, preparation bench, to right	frame 10x10 cm
	Drug room, preparation bench to left	frame 10x10 cm
	Drug room, floor below preparation benches	frame 10x10 cm
	Drug room, sink side of bowl	frame 10x10 cm
	Drug room, drug waste containers	Top brim of two containers total 240 x 2 cm
	Drug room, floor below drug waste containers	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10x10 cm
	Nurse office, floor below door to drug room	frame 10x10 cm
5 / Hematology	Drug room, BSC inside middle	frame 10x10 cm
	Drug room, bench beside BSC	frame 10x10 cm
	Drug room, floor below BSC	Frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Room outside of drug room where waste is handled, top brim of Packtosafe® waste sealing system	frame 10x10 cm
	Room outside of drug room where waste is handled, floor below Pactosafe®	frame 10x10 cm
	Air lock to room for cytostatics, blue basket	frame 10x10 cm
	Room for cytostatics, BSC inside middle	frame 10x10 cm
	Room for cytostatics, top brim of Pactosafe®	frame 10x10 cm
	Room for cytostatics, floor below BSC	frame 10x10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	Frame 10x10 cm
	Nurse office, floor below hand basin	frame 10x10 cm
6 / Hematology-Oncology	Drug room, preparation bench left side	frame 10x10 cm
	Drug room, preparation bench right side	frame 10x10 cm
	Drug room, floor below preparation bench	frame 10x10 cm
	Drug room, drug waste container	Lid and lid handle 30x40 cm
	Drug room, drug waste container	Top of front side 30x20 cm
	Drug room, drug shelf	frame 10x10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10x10 cm
	Nurse office, floor middle	frame 10x10 cm

7 / Infection	Drug room, BSC inside middle	frame 10 x 10 cm
	Drug room, bench beside BSC	frame 10 x 10 cm
	Drug room, floor below BSC	frame 10 x 10 cm
	Drug room, floor below bench beside BSC	frame 10 x 10 cm
	Drug room, top drug waste container under BSC	Front side 30 x 30-25 cm (conical)
	Drug room, bottom drug waste container under BSC	Lid and lid handle 30 x 40 cm
	Drug room, drug shelf	frame 10 x 10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10 x 10 cm
7 / Hematology	Drug room, right preparation bench	frame 10 x 10 cm
	Drug room, left preparation bench	frame 10 x 10 cm
	Drug room, floor below preparation benches	frame 10 x 10 cm
	Drug room, drug waste container	Lid and lid handle 30 x 40 cm
	Drug room, drug shelf	frame 10 x 10 cm
	Patient day room, floor	frame 10 x 10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10 x 10 cm
8 / General ward	Drug room, preparation bench mid-room	frame 10 x 10 cm
	Drug room, preparation bench right	frame 10 x 10 cm
	Drug room, sink side of bowl	frame 10 x 10 cm
	Drug room, floor below preparation benches	frame 10 x 10 cm
	Drug room, drug shelf	frame 10 x 10 cm
	Drug room, drug waste container	Lid and lid handle 30 x 40 cm
	Drug room, floor below drug waste container	frame 10 x 10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame10 x 10 cm
	Nurse office, floor below door to drug room	frame 10 x 10 cm
9 / Infection	Drug room, preparation bench mid-room	frame 10 x 10 cm
	Drug room, preparation bench right	frame 10 x 10 cm
	Drug room, preparation bench left	frame 10 x 10 cm
	Drug room, floor below preparation bench mid-room	frame 10 x 10 cm
	Drug room, floor below drug waste container	frame 10 x 10 cm
	Drug room, drug waste container	Top brim and front side 1x140 cm + 30x60 cm
	Drug room, drug shelf	frame 10 x 10 cm
	Air lock patient ward, drug waste container	Front of plastic bag 20x30 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10 x 10 cm

9 / Hematology	Drug room, preparation bench middle	frame 10 x 10 cm
	Drug room , floor below preparation bench	frame 10 x 10 cm
	Drug room, floor below drug waste container	frame 10 x 10 cm
	Drug room, drug waste container	Lid and lid handle 30 x 40 cm
	Drug room, drug shelf	frame 10 x 10 cm
	Drug room, small bench	frame 10 x 10 cm
	Patient WC, toilet	Seat ring 7 x 60 cm
	Patient WC, floor below toilet	frame 10 x 10 cm
10 / Infection	Drug room, bench opposite to preparation bench	frame 10 x 10 cm
	Drug room, preparation bench	frame 10 x 10 cm
	Drug room, sink side of bowl	frame 10 x 10 cm
	Drug room, floor below preparation bench	frame 10 x 10 cm
	Drug room, drug waste container	Top brim and front side including folded plastic bag 1x160 + 30x20 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, floor below work bench opposite to preparation bench	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, floor below toilet	frame 10x10 cm
11 / Infection	Drug room, preparation bench to left	frame 10x10 cm
	Drug room, preparation bench to right	frame 10x10 cm
	Drug room, sink side of bowl	frame 10x10 cm
	Drug room, floor middle	frame 10x10 cm
	Drug room, waste sack holder	Lid on both sides 2x20x30 cam + edge 1x20x30 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, shelf to left of drug shelf	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, floor below toilet	frame 10x10 cm
12 / Surgery	Drug room, preparation bench by window middle	frame 10 x 10 cm
	Drug room, preparation bench opposite to window middle	frame 10x10 cm
	Drug room, preparation bench in the middle	frame 10x10 cm
	Drug room, floor in the middle	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, drug waste container	Lid 31x24 cm
	Cleaning room, drug waste container	Lid and top brim 30 x 40 cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Room for cytostatics, shelf with cytostatics	frame 10x10 cm
	Room for cytostatics, drug waste container	Top brim 1 x (30+30+40+40) cm

13 / General ward	Drug room, preparation bench to left	frame 10x10 cm
	Drug room, preparation bench to right	frame 10x10 cm
	Drug room, floor below preparation benches	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, trolley	frame 10x10 cm
	Cleaning room, drug waste container	Lid and top brim 40 x 40 cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, floor below toilet	frame 10x10 cm
14 / Hematology	Drug room, preparation bench to left	frame 10x10 cm
	Drug room, preparation bench to right	frame 10x10 cm
	Drug room, floor below preparation benches	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Waste room, drug waste container	Lid and lid handle 40x40 cm
	Waste room, cytostatics waste container	Lid and lid handle 40x40 cm
	Room for cytostatics, preparation bench	frame 10x10 cm
	Room for cytostatics, floor below preparation bench	frame 10x10 cm
	Room for cytostatics, floor below door	frame 10x10 cm
	Patient WC, toilet	Seat ring 7x60 cm
	Patient WC, floor below toilet	frame 10x10 cm
14 / Infection	Drug room, preparation bench on left side	frame 10x10 cm
	Drug room, preparation bench on right side	frame 10x10 cm
	Drug room, floor below preparation benches	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, drug waste container	Top brim 1x(26+26+36+36) cm
	Drug room, waste container in plastics	Lid and lid handle 40x40 cm
	Cleaning room, drug waste container	Top brim 1x(40+40+40+40) cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Cleaning room, bench beside drug waste container	frame 10x10 cm

15 / General ward	Drug room, preparation bench middle	frame 10x10 cm
	Drug room, bench beside preparation bench	frame 10x10 cm
	Drug room, sink beside bowl	frame 10x10 cm
	Drug room, floor below preparation bench	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, floor below sink	frame 10x10 cm
	Drug room, drug waste containers	Top brim of two containers 1x(23+23+19+19) + 1x(39+39+27+27) cm
	Cleaning room, drug waste container	Lid and lid handle 40x40 cm
	Cleaning room, floor below drug waste containers	frame 10x10 cm
	Drug room, waste sack holder	Lid 31x24 cm
16 / General ward	Drug room, BSC inside middle	frame 10x10 cm
	Drug room, bench opposite to BSC	frame 10x10 cm
	Drug room, bench beside the door	frame 10x10 cm
	Drug room, floor below BSC	frame 10x10 cm
	Drug room, floor below bench by the door	frame 10x10 cm
	Drug room, drug shelf	frame 10x10 cm
	Drug room, drug waste container s	Top brim of two containers 2x1x (39+39+26+26) cm
	Cleaning room, drug waste container	Top brim 1x(40x40) cm
	Cleaning room, floor below drug waste container	frame 10x10 cm
	Room for cytostatics, BSC inside middle	frame 10x10 cm
	Room for cytostatics, floor below BSC	frame 10x10 cm
	Room for cytostatics, drug waste container	Lid and lid handle 40x40 cm

Appendix 3.

Examples of preventive measures to minimize the occurrence of spill and leakage

- Consider to change to a closer compounding system. Several studies on spill and leakage during compounding cytostatics have shown that a closed system for compounding minimizes the drug spill and leakage. Also spikes with filter reduce spill and leakage compared with open systems [1].
- Hold the orifice of the tubing over a collection vessel or a bench cover sheet with plastic bottom when filling tubings in infusions systems and not over the floor, bench surface or a sink. Possible drug leakage through the orifice will be then collected on disposal material that can be discarded in a proper waste container, without any emerging spill onto surfaces.
- Prepare as much as possible in the drug room to minimize the risk for spill and leakage in the nursing rooms.
- Use a mixing device for sealed drug vials.
- When possible during administering of antibiotics in pre-compounded infusion bags, start by fill the tubing's of infusion systems with saline solution instead of drug solution before connection to patient infusion port and then end the administration with saline solution to empty all tubing's from the drug solution.

Examples of measures to prevent spatial distribution of emerged spill and leakage

- Use disposal gloves during compounding and change gloves after each compounding to avoid distributing possible spill from one infusion bag to next.
- Carry out the compounding on a bench cover sheet with plastic bottom, e.g. an examination sheet and change/discard the sheet between each compounding. Any spill on the sheet will then not be distributed to next compounding or to bench surfaces.

- Handling tablets can also contribute to distribution of antibiotic substances. To minimize the distribution of tablet dust use disposal gloves and handle the tablets on a bench cover sheet with plastic bottom. Discard the gloves and sheet when the task is finished.

- Discard disposal gloves before leaving the drug room to avoid distribution of drugs through contaminated gloves.

- In case of visible spill, always wipe up the spill everywhere it occur using disposal wipe material. Clean afterwards with water or cleaning alcohol (45% with detergent) before any disinfection with 70% alcohol.

- Most drugs dissolve better in water than 70% disinfection alcohol. Cleaning will, thus, be more efficient if all surfaces are cleaned with water or cleaning alcohol before any disinfection with 70% alcohol.

- If cleaning alcohol (45% with detergent) is regularly used for cleaning a thin film of detergent will be formed and cleaning with pure water will be required on a regular basis

- Improved cleaning can be accomplished by wet mopping twice and change mop in between in places where spill and leakage can occur, e.g., drug room, patient toilettes. A more frequent cleaning can also be required. It is also important to wipe up visible spill and leakage between cleaning occasions and clean with cleaning alcohol or water