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Microbial contamination of pharmaceutical products in the home

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SUMMARY

One thousand, nine hundred and seventy-seven pharmaceutical products used in the home were examined for microbial contamination. Viable micro-organisms were recovered from 14·0% of samples. Medicines used in the home are apparently not exposed to the same opportunities for contamination as those used in hospital.

INTRODUCTION

Considerable work has been carried out in recent years on the microbial contamination of pharmaceutical products and the potential health hazard to users of these products (Kallings *et al.* 1966; Report by a Public Health Laboratory Service Working Party, 1971; Baird, Brown & Shooter, 1976; Baird & Shooter, 1976; Awad, 1977). The published work in most cases has, however, been confined to hospital studies where it may be assumed that pharmaceutical advice and guidance has been given on the use and storage of the products, thereby reducing the risk of microbial contamination. There is no information, by comparison, on the microbial contamination of pharmaceutical products which are used in the home. In this study we describe the results of a microbiological examination of used pharmaceutical products which were collected from homes in the four Thames Metropolitan Regions.

MATERIALS AND METHODS

Collection of samples

Medicines were collected from the four Metropolitan Regions at the same time as a campaign for the disposal of unwanted medicinal products from the home, hereafter referred to as 'Dump', which took place during a 3 week period in October and November 1977. Members of the general public were asked to return all unwanted medicines to their local chemist. Medicines were then taken first to local hospitals in each area and then to a central collecting point for incineration.

Pharmaceutical products were examined on receipt from area hospitals for their suitability for microbiological examination. Only a small number of tablets and capsules were examined in this survey, and comprised those from animal or

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plant extract. With the exception of the latter, solid dosage forms have previously been shown to be relatively free of microbial contamination (Smart & Spooner, 1972). Products which had obviously not been used were discarded. Medicaments were sampled as they would have been used by patients. For example, products in tubes were examined by squeezing out the next sample to be used, even if the tube had a defective or no closure.

Examination of medicaments

Antibacterial agents were neutralized as described previously (Baird *et al.* 1976). Medicaments with no known anti-bacterial agents were sampled into 20 ml of nutrient broth containing 4% Lubrol W. Samples of 1 g or 1 ml of each medicament were added to the appropriate broth and homogenized using a Stomacher 400 (Colworth) where necessary. Broths were incubated aerobically at 37 °C for 24 h, subcultured to horse blood agar and incubated as before. Growth from blood agar was subcultured to MacConkey agar, mannitol salt agar and cetrimide agar 0·03% and organisms isolated were stored on blood agar base slopes at room temperature for identification. Coagulase tests were carried out on all Gram-positive cocci. All Gram-negative organisms were identified using the API 20E identification scheme. Colony counts were carried out in duplicate on nutrient agar on all products from which gram-negative organisms were isolated.

RESULTS

Of the 1977 pharmaceutical products examined, viable micro-organisms were recovered from 277 products (14·0%). Table 1 shows the product types examined and the number found to be contaminated. Oral liquids (in particular mixtures and suspensions) were more frequently found to be contaminated (18·8%) than were liquids for external use (5·2%). Semi-solid topical preparations, such as creams, ointments, gels and pastes, appeared to be equally susceptible to contamination, but were more frequently contaminated (15·8%) than topical liquids. Higher contamination rates (27·5%) were found in solid-dosage preparations for oral and external use (tablets, granules, powders, suppositories, pessaries and dusting powders). This is not as surprising a finding as it might seem, since the tablets were of animal or plant origin and the remaining products had clearly been handled during bulk packaging and use. In the case of suppositories and pessaries, it was evident from the cardboard packaging that most of these had been manufactured some time ago. Certain types of product were more frequently found to be contaminated than others and included those containing kaolin powder, nystatin, hyaluronidase and steroid preparations. Of steroid-containing products, 13·3% were found to be contaminated.

Table 2 shows the micro-organisms isolated from the 277 contaminated products. Aerobic spore bearers and Gram-positive cocci accounted for 90% of all bacterial isolates. *Staph. aureus* was isolated from 13 samples (0·7%) and in all cases from products intended for external use (5 creams, 4 ointments, a paste, a solution, a vaginal cream and a combined ear/eye ointment). Gram-negative organisms

Table 1. *Types of product sampled and number contaminated*

Product	No. of samples	No. contaminated	%
Liquid			
Oral			
Mixture/suspension	163	45	18·8
Linctus	96	11	
Syrup	57	7	
Solution	18	1	
Emulsion	7	2	
Oil	11	0	
External			
Lotion	84	3	5·2
Liniment	17	0	
Solution	23	2	
Paint	21	1	
Oil	8	0	
Inhalant	28	1	
Mouth/spray/gargle	27	3	
Eye drop/lotion	79	2	
Ear drop	78	2	
Nose drop/spray	141	13	
Combined drop	30	1	
Semi-solid external			
Cream			
Skin	462	73	15·8
Vaginal	11	4	
Nasal	5	0	
Rectal	1	0	
Ointment			
Skin	351	64	
Ear/eye	88	7	
Rectal	24	1	
Gel	34	5	
Paste	22	4	
Solid dosage			
Oral			
Tablet/granule/powder	23	11	27·5
External			
Suppository/pessary	23	9	
Powder	39	3	
Miscellaneous	6	2	
Total	1977	277	14·0

were isolated from 28 products (1·4 %), most of which were products for external use, as shown in Table 3. Twelve of these products had been issued by retail chemists, 4 from hospitals, 1 by a doctor and 11 products were of unknown origin. In ten of these products the bacterial counts numbered more than 10^5 organisms/g or ml. *Ps. aeruginosa* was isolated from two re-packed ointments (0·1 %), one of which was a diluted steroid preparation. *Pseudomonas* spp. were isolated from 12 products (0·6 %).

Of the 1977 products examined, 81·6 % were sampled in their original container (as packed by the manufacturer) and 13 % of these were contaminated. A higher contamination rate (20·2 %) was observed in those products which had been

Table 2. *Micro-organisms isolated from 277 contaminated Dump samples*

Product	No. contaminated with: Aerobic spore bearers	Gram-positive cocci	Gram-negative rods
Oral			
Mixture/suspension*	39	4	2
Linctus	6	3	1
Syrup	8	1	—
Solution	—	1	—
Emulsion	2	—	—
External			
Lotion	1	—	2
Solution	—	1	1
Mouth spray/gargle	2	1	—
Eye drop/lotion	2	—	1
Ear drop	2	1	—
Nose drop	10	1	4
Skin cream	22	57	11
Vaginal cream	—	4	—
Skin ointment	22	41	5
Ear/eye ointment	—	7	1
Rectal ointment	—	1	—
Gel	2	3	—
Paste	—	3	—
Solid dosage			
Tablet/granule/powder	10	2	—
Suppository/pessary	3	4	—
External powder	2	—	—
Miscellaneous	—	3	—
Total	133 (6·7%)	138 (7·0%)	28 (1·4%)

* A yeast was isolated from one mixture.

re-packed at the issuing site. Topical preparations packed in pots were rather more frequently found to be contaminated (40 out of 219, or 18·3%) than when packed in tubes (116 out of 786, or 14·8%). During sampling it was observed that several containers were cracked (26) and that a number of containers had defective or no closures (65) or unsuitable closures (13), such as cork. A higher contamination rate (25·9%) was found in these 104 samples.

One thousand six hundred and thirty products had been issued without a date on the sample label (82·4%). Of the 347 products issued with a date, 89 were older than 2 years and 9 were older than 10 years. There appeared to be a small difference between contamination rates in products issued more than 2 years ago (20·2%) and those issued less than 2 years ago (17·3%). None of the products issued more than 10 years ago were found to be contaminated. Of the 1977 products sampled, 17·7% had been issued with an expiry date and 9·6% had expired. Of the expired preparations, 8·0% were found to be contaminated.

On sampling, 1244 products (62·9%) had no issue site marked on the container label; 630 products were of retail origin, 100 had been issued by hospitals and 3 by a doctor. Products issued from retail pharmacies were less often contaminated

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Table 3. *Gram-negative rods found in 28 products*

Product	Contaminant	No. of organisms (per g or ml)
Aludrox mixture	*Citrobacter freundii*	$2{\cdot}4 \times 10^5$
KLN mixture	*Enterobacter agglomerans*	$< 10^2$
Benylin Co. linctus	*E. agglomerans*	$< 10^2$
Vioform hydrocortisone lotion	*Achromobacter xylosoxidans* *Serratia liquifaciens*	$> 10^6$
Vioform hydrocortisone lotion	*Serratia liquifaciens*	$4{\cdot}6 \times 10^5$
Balsam shampoo	*Ps. cepacia*	$3{\cdot}7 \times 10^3$
The eye lotion	*Pseudomonas* spp.	$4{\cdot}0 \times 10^4$
Ephedrine nose drop	*Ps. maltophilia*	$1{\cdot}2 \times 10^6$
Ephedrine nose drop	*Kleb. pneumoniae*	$1{\cdot}5 \times 10^6$
Otrivine nose drop	*Ps. putida*	$5{\cdot}8 \times 10^5$
Otrivine nose drop	*Pseudomonas* spp.	$< 10^2$
Lanolin cream	*Enterobacter agglomerans*	$< 10^2$
The cream	*Ps. fluorescens*	$1{\cdot}6 \times 10^3$
Hydrocortisone cream	*Enterobacter cloacae*	$1{\cdot}3 \times 10^3$
Hydrocortisone cream	*Kleb. pneumoniae*	$2{\cdot}5 \times 10^2$
Hydrocortisone cream	*Ps. fluorescens*	$7{\cdot}3 \times 10^5$
The cream	*Ps. putida*	$> 10^6$
Halciderm cream	*Enterobacter agglomerans*	$< 10^2$
Skin cream	*E. agglomerans*	$< 10^2$
Savlon cream	*Pseudomonas* spp.	$< 10^2$
Belnovo cream	*Enterobacter* spp.	$7{\cdot}9 \times 10^3$
Calamine cream	*Ps. pseudoalcaligenes*	$3{\cdot}5 \times 10^4$
Tyrotrace ointment	*Enterobacter cloacae*	$< 10^2$
Betnesol 1 in 10 ointment	*Ps. aeruginosa*	$> 10^6$
Lasonil ointment	*Ps. fluorescens*	$< 10^2$
The ointment	*Ps. aeruginosa*	$> 10^6$
Molivate ointment	*Ps. stutzeri*	$< 10^2$
Albucid eye ointment	*Enterobacter agglomerans*	$< 10^2$

(14·9%) compared with those issued by hospitals (21%). There appeared to be no difference, however, in the type of contaminants isolated from products issued from both these sites; aerobic spore bearers, Gram-positive cocci and Gram-negative rods were isolated from both groups. Of the 1977 products sampled, 365 contained a preservative and 507 contained antimicrobial agents (antibacterial, antifungal and antiviral agents), as indicated on the package. A lower contamination rate was observed in these products (8·1%) compared with those products with no such antimicrobial agents stated on the label (18·7%).

DISCUSSION

One of the main problems encountered in this survey was the absence of microbiological information on all samples at the point of issue. It was thus impossible to state with any degree of certainty whether the contamination had arisen during manufacture in industry or in hospital, or whether it had arisen during use of the product. The fact that products issued from hospitals were more frequently contaminated than those issued from retail suggests that at least some of these products were contaminated when issued. This was confirmed in a small pilot

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study of 200 different types of unopened pharmaceutical products and where 7·5% of products were found to be contaminated. There appeared to be no difference, however, between repacked contaminated products issued from hospitals (10 out of 21) and from retail (48 out of 96). As in other surveys (Report by a Public Health Laboratory Service Working Party, 1971; Baird & Shooter, 1976), the practice of repacking products into smaller packs was associated in this study with an increased likelihood of contaminating the product before issue.

Despite the fact that all products were examined before sampling, it was impossible to tell by appearance whether products had been used in 106 cases. During the course of the 'Dump' campaign, it was observed that a large number of unopened expired products were returned from retail chemists and it is possible that some of these products were sampled inadvertently in our survey. This may account for the relatively small number of expired products which were found to be contaminated (5·4% of the total number of contaminated products). It may also suggest that some of the older products were inherently less susceptible to contamination compared with some of the newer formulations.

A useful comparison can be made between the results of this survey and results obtained from studies of pharmaceutical products made and used in hospitals.

Contamination rates in unused hospital-produced pharmaceuticals have been found to vary between 7 and 32%, according to the environmental conditions where the product is made (Baird, Parks & Awad, 1977). The Public Health Laboratory Service in 1971 reported a contamination rate of 32% in pharmaceutical products examined during use in hospital wards. More recently, Awad (1977) found similar contamination rates in products examined after use on their return to the pharmacy (31%). The lower contamination rate for medicines in our survey (14·0%) may be explained by the fact that medicines in the home are not exposed to the same opportunities for contamination as those in hospitals. The fact that domiciliary medicines are generally issued in reasonably small quantities for use by one person must bear some consideration. In spite of a rapid turnover in hospitals, stock bottles and pots may be used on several patients and may become contaminated during the many openings and closings of the container.

The presence of Gram-negative organisms in pharmaceutical products and their significance to the patient has attracted much attention in recent years. It is generally agreed that the presence of free-living opportunist pathogens (such as those found in this study) is undesirable. This is particularly so when the organism is present in high bacterial numbers and in certain types of products, such as those containing steroids (7 out of 14 topical preparations in this study) and those for ophthalmic use (two products).

The presence of *Pseudomonas* in used pharmaceutical products examined in hospitals has been noted in the past. The PHLS (1971) reported isolation rates of 8·9% for *Pseudomonas* spp. and 2·7% for *Ps. aeruginosa;* the latter was found exclusively in hospital pharmacy containers. In the present study *Ps. aeruginosa* was isolated from two products only (0·1% of samples), neither of which had originated from hospitals; *Pseudomonas* spp. were isolated from 12 products (0·6%). This low incidence may be partly explained by the fact that only a small

number of samples had originated from hospitals (5% of those products where the issuing site could be determined). Another contributory factor may be an increased awareness of the importance of *Ps. aeruginosa* in pharmaceutical products and a general improvement seen in microbiological standards in recent years. A more significant factor may, however, be that *Ps. aeruginosa* is apparently isolated rarely from the domestic environment (Whitby & Rampling, 1972).

One finding from this survey which merits comment was the apparent lack of information given to outpatients on the correct usage, storage conditions and the appropriate shelf life of pharmaceutical products used in the home. The fact that 82% of samples had no issue date nor expiry date marked on the label and that 63% of samples had no labels with instructions for use of the product, suggests that much more guidance could be issued to the general practice patient. Information issued by manufacturers, such as the expiry date, is frequently stamped only on an outer carton which may be discarded when the product is issued. Although there appeared to be no evidence in this survey that the microbiological quality of the medicines was affected by storage for long periods in the home, clearly this is an important consideration from the pharmaceutical point of view. In view of the tendency to hoard medicines in the home, it is recommended that expiry dates should be marked on the product container itself. Similarly, relevant information given at the issuing site on the correct usage and storage conditions for the product should be attached to the product container.

Clearly, the results from this study gave no information on the possible adverse effects on the user of contaminated pharmaceutical products. One suggestion which the practitioner may consider is that the microbiological examination of medicines used in the home may provide useful information, particularly in the treatment of recurring eye and ear infections.

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