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A review of the *in vitro* and *in vivo* valved holding chamber (VHC) literature with a focus on the AeroChamber Plus Flow-Vu Anti-static VHC

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***Abstract*:** Valved holding chambers (VHCs) reduce the need for inhalation-actuation coordination with pressurized metered dose inhalers (pMDIs), reduce oropharyngeal drug deposition and may improve lung deposition and clinical outcomes compared to pMDIs used alone. While VHCs are thus widely advocated for use in vulnerable patient groups within clinical and regulatory guidelines, there is less consensus as to whether the performance differences between different VHCs have clinical implications. This review evaluates the VHC literature, in particular the data pertaining to large- *versus* small-volume chambers, aerosol performance with a VHC adjunct *versus* a pMDI alone, charge dissipative/conducting *versus* non-conducting VHCs, and facemasks, to ascertain whether potentially meaningful differences between VHCs exist. Inconsistencies in the literature are examined and explained, and relationships between *in vitro* and *in vivo* data are discussed. A particular focus of this review is the AeroChamber Plus® Flow-Vu® Anti-static VHC, the most recent iteration of the AeroChamber VHC family.

Keywords: Aerochamber Plus, aerosol holding chambers, inhalation spacers, valved holding chambers

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Introduction

The use of spacing chambers is now firmly established within the therapeutic paradigm. Spacers and valved holding chambers (VHCs; which include a one-way inhalation valve) allow deceleration of the aerosol plume and, in the case of VHCs, trap the aerosol cloud until the patient inhales. This reduces oropharyngeal drug deposition by approximately 80–90% *via* retention of large aerosol particles within the holding chamber[1–3] and for VHCs substantially lessens the requirement for coordination between pMDI actuation and inhalation,[4] which is problematic in approximately one-third of subjects using a pMDI.[5,6] As a result, VHCs may increase pulmonary drug deposition[7–9] and in comparison to pMDIs used alone, pMDI/VHC combinations have been shown to improve airway hyperresponsiveness,[10] lung function[11–14] and asthma control,[15] afford greater withdrawal of oral corticosteroids,[16] and reduce the local[16] and systemic side effects[17–19] of inhaled corticosteroids. Accordingly, virtually all national and international obstructive lung disease guidelines now advocate the use of spacers/VHCs in patient subgroups prone to pMDI handling errors,[20–28] with spacer usage also specifically stipulated for inhaled corticosteroid administration within key national guidance documents.[21,24,25,28]

While the potential benefits of VHCs are clear, there is less consensus as to whether meaningful differences exist between different devices. Thus, while the Global Initiative for Asthma notes that performance differences may exist between different spacers,[26] sentiments echoed within the EU Orally Inhaled Product guideline,[29] similar

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statements are lacking in other clinical or regulatory authority guidance documents. This discordance may reflect the multitude of different VHCs that are currently marketed, many of which superficially resemble one another, allied to a large body of (principally *in vitro*) data, some of which are seemingly in conflict.

Aims

The purpose of this review was to examine the available data regarding the AeroChamber Plus® Flow-Vu® anti-static VHC (AC+FV aVHC) in the context of the related VHC literature. The AC+FV aVHC is the most recent iteration of the widely available AeroChamber Plus range of VHCs which are currently the most employed VHCs globally. The review focuses on specific facets of VHC design and performance with the potential to impart meaningful differences between VHCs *in vivo*. Where the literature was seemingly in conflict we sought to understand why this might be. Note that although the terms 'spacer' and 'valved holding chamber' are frequently used interchangeably, a simple spacing device that lacks a one-way valve is susceptible to dispersal of the aerosol within due to uncoordinated exhalation into the chamber. Thus, VHCs are preferred and will be the focus of this review.

Background

The AeroChamber Plus VHC was first introduced in 1983. Since that time there have been several modifications to the VHC intended to improve product performance and/or usability. These include the introduction of: a range of patient-/age-specific facemask VHC products; an 'inspiratory flow indicator', or Flow-Vu, moving in accord with inspiration and expiration in the presence of an adequate mouth or facemask seal; an alert whistle intended to indicate the attainment of excessive inspiratory flow rates (limited to adult versions of the device); and most recently in 2009 a charge dissipative version (the primary focus of the present review) of the same dimensions and comprising the same polymer as the parent VHC but with the addition of an anti-static resin.

Further to the various device iterations detailed above, two AeroChamber variants are currently available: the non-conducting AeroChamber Plus VHC (AC+ VHC) and the charge dissipative AeroChamber Plus Flow-Vu anti-static VHC (AC+FV aVHC) (Figure 1; facemask versions shown). A considerably greater body of data is available for the non-conducting VHC, given its earlier inception. Importantly, however, when interpreting the published data, the performance of these two AeroChamber Plus devices is essentially the same *in vitro* – where the non-conducting variant is pre-treated per the manufacturer's instructions (i.e. washed in a warm detergent solution and then air-dried) and where the anti-static version has had no such pre-treatment (the anti-static resin precludes the need for the patient to perform this step). Under such conditions total emitted mass and fine particle dose (FPD) from eight commonly used pMDIs was essentially the same for the AC+ VHC and AC+FV aVHC.[30] These data also imply that the inspiratory flow indicator incorporated within the AC+FV aVHC design has no effect upon the aerosol pathway within the VHC.

Figure 1. AeroChamber Plus® valved holding chamber (AC+ VHC) and AeroChamber Plus® anti-static valved holding chamber (AC+ aVHC) (facemask versions).

Methods

The PubMed database was searched for the term 'valved holding chamber' in conjunction with any of the following: 'volume', 'static', 'delay', 'mask', 'facemask', 'seal', 'asthma' and 'COPD'. These terms were selected on the basis of their known relevance to VHC performance and, with respect to the disease terms, the intended focus of this manuscript upon obstructive lung disease. The search

was limited to comparative studies with particular attention paid to studies that included the AeroChamber Plus VHC in any of its iterations.

Abstracts of all relevant papers identified during this search were reviewed, and any papers of potential interest were reviewed in full. Citations of particular relevance within these initial papers were also identified and subsequently reviewed. Note that this review was not intended to exhaustively detail every available study in the field, but rather to critically appraise the key publications and distil learning points detailed therein.

Results

Spacer volume

There has been much debate as to ideal VHC dimensions, although in more recent years attention has switched to other facets of VHC design.

In an *in vitro* study of seven different spacing chambers, washed in water alone, differences in drug delivery between devices were highly dependent upon the formulation in question. Thus there was a marked difference in sodium cromoglycate FPD delivered *via* the AC+ VHC (145 ml) compared to the Nebuhaler® (750 ml), in favour of the latter, whereas no difference between these VHCs in terms of budesonide FPD was evident. Nonetheless, overall the larger volume spacing chambers in this *in vitro* study (the Fisonair, Nebuhaler, Volumatic® and Inspirease) performed better than their smaller volume counterparts [the AC+ VHC, Aerosol Cloud Enhancer (ACE®) and Dynahaler®].[31] Somewhat similar results were reported in a pharmacokinetic study of a salbutamol hydrofluoroalkane (HFA) formulation in which spacers were again washed in water alone: pulmonary salbutamol delivery *via* the Nebuhaler (750 ml) exceeded that *via* the AC+ VHC by 63%, although no difference was noted between the Volumatic (750 ml) and AC+ VHC.[32] An earlier scintigraphic comparison also supported the notion of greater drug delivery from large-volume VHCs *versus* the AC+ VHC,[33] while a further *in vitro* study showed somewhat greater salbutamol small particle output (<6.8 μm) with a large-volume Nebuhaler than with three smaller non-conducting VHCs when all devices were detergent-washed.[34]

Other studies have yielded results in contrast with the above. Two *in vitro* studies reported equivalent FPD outputs *via* detergent-washed Volumatic and AC+ VHCs for an HFA fluticasone pMDI[35] and both components of an HFA fluticasone/salmeterol formulation.[36] Similar pulmonary delivery of these same formulations *via* the Volumatic or AC+ VHC was also suggested by a series of adrenal axis studies where VHCs were pre-washed with detergent and/or effectively primed *via* the administration of multiple drug actuations.[37–41] In a further pharmacodynamic study, the short-term growth suppressive effect of HFA beclometasone (reflective primarily of pulmonary beclomethasone delivery) was similar whether delivered *via* an AC+ VHC or Volumatic,[42] again where both VHCs were detergent-washed (personal communication, Ole Wolthers).

Interpretation of these sometimes conflicting data is hampered by a lack of detail in earlier studies as to whether CFC or HFA formulations were employed, although the absence of such detail likely implies the former. Nonetheless, and while the active substance in question and factors such as airflow recirculation and valve design may also be relevant,[43] it would appear that performance differences between large- and small-volume VHCs are less evident with HFA *versus* CFC formulations, as has been demonstrated for salbutamol formulations,[44,45] and where non-conducting spacers are afforded an anti-static coating. These observations would appear intuitive. A slower (and/or narrower) HFA aerosol plume is liable to be more forgiving of a shorter chamber or narrower chamber diameter, while an anti-static coating would also be expected to mitigate the effects of smaller chamber dimensions.

Currently there are no data which compare the effect of the AC+FV aVHC *versus* that of a large-volume VHC upon a particular formulation. However, based on the preceding discussion, it would be anticipated that the delivery of contemporary aerosols *via* the AC+FV aVHC would be broadly similar to that *via* a large-volume chamber. This is further suggested *via* the comparison of two different HFA fluticasone-containing formulations (fluticasone monotherapy and fluticasone/formoterol) with similar *in vitro* characteristics, in a recent pharmacodynamic study. With the monotherapy administered *via* the Volumatic and the combination *via* the AC+FV aVHC, virtually identical effects upon lower leg growth rate were observed.[46]

Performance in comparison to the pMDI

A key clinical consideration when choosing a pMDI/VHC combination is the likely impact of the VHC upon pulmonary drug delivery, it being virtually assured that the oropharyngeal dose will be substantially attenuated irrespective of VHC selection *via* removal of the ballistic aerosol fraction.[3,7,47] Importantly, a VHC should not materially reduce pulmonary drug delivery in comparison to a pMDI alone. Despite this, some studies have demonstrated potentially important reductions in the respirable drug dose with certain VHCs. For example, the FPD of an salbutamol pMDI was shown to be reduced by 36% *via* a puff-primed ACE VHC, but was essentially unchanged for the three other VHCs tested.[48] In another study the FPD of a fluticasone/formoterol pMDI was substantially reduced when delivered *via* a metal Vortex® VHC.[49] Conversely, *in vitro*[44] and *in vivo*[50] studies have demonstrated that the Nebuhaler VHC may result in a lung dose 2–3 times that *via* a pMDI alone.

Turning to the AC+FV aVHC, *in vitro* data demonstrate that the FPD delivered *via* this VHC is comparable to that delivered *via* the pMDI alone, albeit the exact relationship with/without the VHC depends upon the formulation in question. The FPD ratio for eight HFA formulations (comprising 10 active substances) delivered *via* the AC+FV aVHC *versus* the pMDI alone ranged from approximately 120% to 160% where there was no delay between actuation and sampling.[30] Similar results were reported in other studies of salbutamol and beclomethasone/formoterol pMDIs.[51,52] Importantly, where a 2 s delay in sampling was imposed for the AC+FV aVHC, simulating use by a more representative semi-coordinated patient, the FPD remained similar to that *via* a pMDI coordinated perfectly (FPD ratio approximately 85–120%).[30]

Comparable results to the above have also been reported for the older AC+ VHC where prewashed in detergent solution and air-dried (personal communication, Geraldine Venthoye).[30,36,49] Further, other than the removal of the coarse particle fraction that would otherwise be deposited in the oropharynx, aerosol particle size distribution is essentially unchanged with delivery *via* the AC+ VHC or pMDI alone,[36,49,51] implying similar regional pulmonary deposition will ensue. The latter is an important observation since there has been much focus upon optimal aerosol particle size, which may differ according to the therapeutic class of the inhaled drug[53–57] and is also relevant to deposition efficiency (i.e. the proportion of inhaled particles which successfully deposit in the lung rather than impacting in the oropharynx or being exhaled prior to sedimentation).[58,59] While competing hypotheses as to optimal particle size exist,[60,61] it is important that prescribers selecting a given pMDI, based at least in part on its particle size character can anticipate similar performance in conjunction with a VHC.

Taken together, the *in vitro* data above imply that equivalent clinical deposition/effects would be seen with a pMDI used optimally or in conjunction with the AC+FV aVHC/detergent-washed AC+ VHC. Accordingly, comparable pulmonary deposition *via* a pMDI with and without the AC+ VHC spacer has been demonstrated in three scintigraphic studies.[1,2,47] Interestingly, in none of these studies was prewashing of the AC+ VHC reported, hence lung deposition with the AC+ VHC may have been less than maximal. Similar drug delivery with and without the AC+ VHC has also been reported in pharmacokinetic studies, another tightly controlled setting.[62,63] However, in patients where pMDI technique is poor and in whom disease control is accordingly less likely to be adequate,[64,65] clinical outcomes would be expected to improve where an AC+ VHC is employed, since in such patients the lung dose is markedly increased with AC+ VHC use.[66] This is likely to explain the significant reduction in oral corticosteroid usage reported by Salzman and Pyszczynski in oral prednisolone-dependent patients receiving beclomethasone *via* an AC+ VHC compared to a pMDI alone.[16] These patients by their nature were likely to include a large proportion with imperfect inhaler technique. More surprisingly, perhaps, given the highly controlled nature of the study involved, mild to moderate asthmatics receiving supra-therapeutic single doses of fluticasone *via* a prewashed AC+ VHC or a pMDI alone exhibited substantially greater adrenal axis suppression in the AC+ VHC arm, reflective of higher pulmonary drug delivery.[40] Although this difference may have been exaggerated by the pMDI group sitting on the cusp of a steep dose–response curve, it does nonetheless illustrate the potential for *in vitro–in vivo* discordance most plausibly explained by suboptimal clinical handling of the pMDI.

In summary, therefore, while the *in vitro* data indicate that the AC+FV aVHC and pre-washed AC+ VHC perform comparably to the pMDI alone, a direct *in vivo* translation of these data is most realistic in patients with optimal inhaler technique. In patients whose pMDI technique is less ideal, increased pulmonary deposition *via* the use of these VHCs would be anticipated. However, this increased exposure corresponds only to that anticipated in patients with good pMDI handling capability. As such, no amendment to doses recommended *via* pMDIs are required for the AC+FV aVHC, although individualized dose titration dependent upon treatment response should be employed as usual. Importantly, regional pulmonary deposition would be expected to be unchanged with the AC+FV aVHC.

Charge dissipative/electrical conducting spacers

A substantial proportion of the 'respirable dose' of an aerosol will potentially be lost within a non-conducting VHC (made, for example, from polycarbonate or polyester) as a result of electrostatic interactions between aerosol particles and the VHC's internal walls. This is a result of charge acquisition by the VHC during manufacture, storage and packaging, and as a result of triboelectrification (frictional charging) of aerosol formulations during their passage out of the canister *via* a metering valve.[67]

Multiple *in vitro* and *in vivo* studies have demonstrated that drug delivery from non-conducting VHCs is typically improved by pre-washing in a detergent solution and air-drying, or *via* other means of anti-static coating.[68–73] Of note, however, the relative effects of detergent coating may differ for different non-conducting VHCs[34,74,75] and for different active substances/formulations.[76] Thus, for example, with a 2 s testing delay, the FPD emitted *via* a detergent-washed Pocket Chamber® was decreased to half that *via* an unwashed Pocket Chamber; whereas in the same study detergent washing increased the FPD output for another non-conducting VHC, the ProChamber®, approximately twofold.[74] In another study, detergent washing of a Babyhaler had varying effects upon FPD output dependent upon the active substance and product strength.[76] Furthermore, the efficiency of priming *via* multiple inhaler actuations has been reported to differ for the same formulation/non-conducting VHC combination across different studies.[75,77] Lastly, even where a detergent coating can provide a highly effective anti-static coating for a given VHC, patient behaviours may mitigate against this. Approximately 50–60% of patients are reported to wash their VHCs in water (some doing so after each use), while 25–70% towel-dry their VHCs post-washing.[69,78] Wildhaber and colleagues even noted that one-quarter of patients kept their spacers wrapped in plastic bags.[69]

Two approaches have been employed to circumvent such inconsistencies and behaviours: the use of electrical conducting metal chambers, such as the Nebuchamber or Vortex; or alternatively that of charge dissipative plastic spacers such as the AC+FV aVHC or OptiChamber® Diamond. The advantage of the latter is that they allow visualization of the aerosol plume through the VHC.

Aerosol half-life within the metal Nebuchamber substantially exceeds that of unconditioned non-conducting VHCs (including the AC+ VHC) and, in contrast to non-conducting chambers, remains unchanged when the Nebuchamber is washed or primed with repeated aerosol actuations.[71,75,77] Given its anti-static character and prolongation of aerosol half-life, FPD output *via* the Nebuchamber unsurprisingly exceeds that of non-washed non-conducting VHCs when tested with and without sampling delays.[34,77,79] Similar results have been observed with the metal Vortex VHC and the charge dissipative AC+FV aVHC, Pocket Chamber and AeroChamber MAX® [a slightly larger (198 ml) antecedent of the AC+FV aVHC].[74,80] Thus, Suggett and colleagues reported a fluticasone FPD of 40 µg *via* the AC+FV aVHC and 25 µg *via* the Pocket Chamber compared to a FPD of less than 5 µg for three non-conducting VHCs (Compact SpaceChamber Plus®, Breath-A-Tech™ and PrimeAire®). Even following detergent washing, significant differences in FPD output were seen between the Compact SpaceChamber Plus and PrimeAire *versus* the AC+FV aVHC.[80]

In a further experiment, Suggett and colleagues evaluated the total emitted drug mass where fluticasone pMDI actuation into the detergent-washed VHCs was timed to coincide with the onset of inhalation (simulating a perfectly 'coordinated' patient) or the onset of exhalation (a worst-case 'uncoordinated' patient). Notably, total emitted mass was greatly reduced for the

anti-static Pocket Chamber and non-conducting PrimeAire to a clinically relevant degree in the uncoordinated *versus* coordinated simulation, but not for the AC+FV aVHC, Compact SpaceChamber Plus or Breath-A-Tech. The 'uncoordinated' total emitted mass with the AC+FV aVHC thus markedly exceeded that with the anti-static Pocket Chamber ($p < 0.001$) [as well as that with the PrimeAire ($p < 0.001$)]. These data, which reflect differences in the effectiveness of the respective VHC valving,[67] thus illustrate differences between different anti-static VHCs, and between different non-conducting VHCs, in terms of their vulnerability to imperfect patient coordination.[80] Another example of differences in valving effectiveness is available from Sharpe and colleagues, who compared an out-of-package AC+FV aVHC to a pre-treated A2A Spacer®. The total emitted mass was reduced by 44% for the A2A but was unchanged for the AC+FV aVHC with 'uncoordinated' *versus* 'coordinated' pMDI actuation.[81]

The resilience of the AC+FV aVHC performance to prolonged sampling delays has also been demonstrated: with sampling delays of 2, 5 and 10 s the FPDs *via* the AC+FV aVHC following actuation of a fluticasone pMDI were 42, 40 and 36 μg, respectively. In contrast, FPDs for the Optichamber Diamond, another anti-static VHC, at the corresponding sampling timepoints were 35, 29 and 23 μg, respectively – significantly lower than for the AC+FV aVHC at the two later time points.[82] Minimal aerosol losses with the AC+FV aVHC over a 10 s period were again shown in a later study.[83] These data therefore once again illustrate the potential for differences in performance between different anti-static VHCs.

As summarized above, overt performance differences exist between anti-static and non-conducting VHCs. These have translated to large differences in *in vivo* lung deposition studies.[72,73,84] Thus meaningful differences in clinical outcomes would be expected to ensue. To date there are few clinical studies that have evaluated this hypothesis. However, those that have been undertaken are instructive. Dompeling and colleagues[85] and Dubus and colleagues[86] both failed to show differences between anti-static and non-conducting VHCs in their respective studies. In Dompeling's paediatric study no PEFR differences were evident following salbutamol delivery *via* the Volumatic, AC+ VHC or metal Nebuchamber.[85] These results are, however, unsurprising given the notoriously shallow spirometric dose response for β-agonists[87,88] allied to a population with near-normal baseline lung function. Similarly, in Dubus' study, no differences in specific airway resistance (sRaw) or FEV1 were seen following a methacholine challenge in children administered salbutamol *via* a non-conducting Babyhaler, a detergent-washed Babyhaler or a metal Nebuchamber.[86] While comments as to β-agonist dose response are again relevant, results from this study are perhaps more surprising as airway challenge (bronchoprovocation) studies typically offer greater potential for dose response than conventional spirometric indices.[89,90] However, detergent washing may confer variable and unpredictable anti-static effects upon the Babyhaler[75] which, in addition to a pMDI that fitted poorly into the Nebuchamber, the obfuscation of late treatment differences by a cumulative dosing protocol and a suboptimal parallel group design, may explain the apparent lack of additional benefit from the anti-static VHCs in Dubus' study.

Two recent studies have been more encouraging. Prabhakaran and colleagues compared the anti-static AeroChamber Plus Z-Stat® (functionally very similar to the AC+FV aVHC but comprising a slightly opaque base polymer and lacking an inspiratory flow indicator) to the non-conducting AC+ VHC in adults with nocturnal asthma,[91] a phenotype that exhibits a prominent nocturnal decrease in lung function.[92] Mean percentage predicted FEV1 values in the AeroChamber Plus Z-stat and AC+ VHC arms, respectively, after 1, 2 and 4 salbutamol puffs were 52% *versus* 30%, 73% *versus* 48% and 90% *versus* 64%.[91] While these results are striking, the population studied represent a highly selected asthmatic phenotype. However, as noted by the authors, these data may imply potential benefits from using anti-static VHCs in the emergency room setting for acute asthma, and warrant further evaluation.

Another recent study is therefore of particular interest, given its real-world setting. Such studies have generated increasing attention in recent years[93–95] due to their broad generalizability in contrast to conventional randomized, controlled trials. In a retrospective database study the clinical outcomes of two matched cohorts, the AC+FV aVHC cohort and the 'any non-anti-static' VHC cohort, were examined. Each cohort comprised over 9000 subjects, 86% of whom were under 18 years of age. Over 12 months, compared to the 'any non-anti-static VHC' cohort, in the AC+FV

aVHC cohort the annualized rate of moderate to severe exacerbations (defined as claims for oral corticosteroids, emergency room visits or in-patient admission for asthma) was reduced by 10% ($p = 0.067$), the time to first moderate to severe exacerbation was prolonged ($p = 0.0005$) and the incidences of ER visits (relative reduction 13%; $p = 0.017$) and hospitalizations (relative reduction 19%; $p = 0.072$) were reduced.[96] This study thus appears to link the *in vitro* VHC differences discussed earlier (such as the impact upon FPD of using untreated non-conducting VHCs) and clinical outcomes. In the light of these promising results, it is of note that compliance with spacer usage is reported to be poor,[97,98] which would be expected to bias towards equivalence between VHCs. It would be of considerable interest therefore to evaluate treatment differences between the AC+FV aVHC and non-conducting VHCs in a setting in which satisfactory levels of compliance could be assured, and in a population with more frequent exacerbations, as exacerbation frequency in the primarily paediatric/adolescent population evaluated by Burudpakdee and colleagues was relatively low.[96] Under such circumstances it is plausible the differences between anti-static and non-conducting VHCs would be amplified.

Facemasks

Alongside measures to minimize static-related aerosol losses, facemasks are arguably the most important components of VHC systems. Expert consensus is that an ideal facemask should: facilitate a tight seal; incorporate minimal deadspace; be composed of a soft polymer and have a contoured rolled edge; reflect the facial contours of intended patient subgroups; and contain a low-resistance exhalation valve directing exhaled air away from the VHC.[99]

Several studies have demonstrated the criticality of a tight facemask seal.[100–103] For example, a facemask leak near the nose of only 0.4 cm^2 has been shown to reduce lung delivery from 10% of the labelled dose to zero.[101]

In young children whose parents employed their usual VHC/facemask technique, the AC+ VHC facemask was shown to provide a seal as tight as that of the 'gold standard' Hans Rudolph anaesthetic mask, while the Nebuchamber mask provided the most porous seal. The authors attributed these results to the sharp, flat and relatively rigid edge of the Nebuchamber mask in contrast to the rounded, flexible edges of the other masks tested.[102] In contrast to these results, in a recent *in vitro* study employing a facemask force of 1.9 kg, Xu and colleagues reported a substantial leak from the anti-static AeroChamber Z-Stat VHC/ComfortSeal® facemask that considerably exceeded that from the anti-static Optichamber Diamond VHC/LiteTouch® facemask. Accordingly, drug delivery *via* the OptiChamber Diamond/LiteTouch exceeded that *via* the AeroChamber Z-Stat/ComfortSeal.[104] The incongruity between the results from the above two studies suggests either that positioning of the AeroChamber ComfortSeal facemask in Xu's study was suboptimal, or that the ComfortSeal facemask requires a greater force applied to it than the Litetouch in order to facilitate a good seal.

Comparative *in vitro* testing of the AC+FV aVHC/ComfortSeal mask and the OptiChamber Diamond VHC/LiteTouch mask in two further studies,[105,106] employing a lesser facemask force (1.6 kg) than in Xu's study suggests positioning may have been the primary issue in the latter. Correct positioning of each VHC facemask was confirmed by Sharpe and colleagues and DiBlasi and colleagues prior to pMDI actuation by positioning the facemask to optimize flow through the model system (personal communication, Mark Nagel). Note that in both of these studies, although the same ComfortSeal mask was used as by Xu and colleagues, unlike in Xu's study the AeroChamber model evaluated was the AC+FV aVHC, which includes a Flow-Vu inspiratory flow indicator. The latter comprises an enclosed flap atop the VHC that moves towards and away from the patient in synchrony with inhalation and exhalation, but does so only in the presence of a good seal. Thus adjustments can be made to facemask positioning to establish a satisfactory seal if one is not immediately attained. In both Sharpe's and DiBlasi's AC+FV aVHC studies, a greater delivered mass of drug was seen with the AC+FV aVHC/ComfortSeal mask than with the OptiChamber Diamond/LiteTouch.[105,106] The discordance between these data and those of Xu and colleagues[104] illustrates the real-world utility of a simple feedback mechanism, such as the inspiratory flow indicator, which facilitates an intuitive assessment of facemask positioning and seal integrity.

The practical benefit of the inspiratory flow indicator is further supported by a paediatric clinical

study that compared the AC+ VHC and AC+FV aVHC for administering inhaled corticosteroid therapy.[107] The mean improvement in the paediatric asthma caregiver's quality of life questionnaire (PACQLQ) exceeded the minimum clinically important threshold[108] in the AC+FV aVHC group, but not the AC+ VHC group. The PACQLQ data were in accordance with device preference data, which indicated a strong preference among caregivers for the AC+FV aVHC ($p < 0.001$). This is likely attributable to the inspiratory flow indicator as the most visible external difference between VHCs, and is an important finding since correct usage of, and adherence to, inhaled treatment are associated with ease of use and preference.[109–111]

Mask deadspace is a further important consideration in infants, given their low tidal volumes. For example, in a 6-month-old infant, tidal volume is approximately only 55 ml. With such a tidal volume, increasing mask deadspace by approximately 50 ml may thus reduce aerosol delivery by 60%.[112]

Shah and colleagues evaluated mask deadspace and seal integrity for seven commercially available VHC/mask combinations, applying three different forces to each facemask.[113] The AC+ VHC, Optichamber and Vortex masks exhibited the lowest deadspace volumes at all three forces (⩽48 ml), and at 0.7 kg and 1.6 kg force were the only masks with deadspace volumes below the tidal volume of a 6-month-old infant. However, only the AC+ VHC and Optichamber masks formed seals at a low (0.7 kg) force, while the stiffer Vortex (the second stiffest of the masks tested) required a high force of 3.2 kg to establish a seal. Deadspace volume was decreased with increasing force (for all but the stiffest Pocket Chamber mask), with the greatest decrements noted for the most flexible masks: the Easivent®, ACE, and AC+ VHC. Unlike the AC+ VHC however, the Easivent and ACE required forces of 3.2 kg to provide to an acceptably low deadspace volume. Overall, therefore, while this study demonstrated that five of the seven masks tested could potentially provide an appropriate deadspace volume and seal, only the AC+ VHC and Optichamber masks did so with low and medium applied forces. These are important findings since forcefully applying a mask to a young child's face will inevitably lead to distress, crying and noncompliance, such that the likelihood of attaining a good seal will be negligible and aerosol delivery will be greatly diminished.[114,115]

In summary, the available comparative data that are principally *in vitro* indicate that the composition and design of the AC+FV aVHC/ComfortSeal are well suited to providing a good seal and minimizing deadspace, and compare favourably with other marketed VHC/facemask delivery systems. Further, although not explicitly detailed above, the AC+FV aVHC/ComfortSeal complies with other aspects of ideal facemask design as identified at the International Society for Aerosols in Medicine (ISAM) Focus Symposium.[99]

Conclusion

There is substantial, occasionally contradictory, literature detailing the relative performance of a large number of different VHCs. During the early development of these devices much of the focus was upon their respective dimensions and shape. As VHC design has become more sophisticated and understanding of clinically relevant testing conditions has evolved, emphasis has shifted to other aspects of performance, prominent among which are consistency of drug delivery under a variety of test conditions, the influence of conducting or charge dissipative materials, and the factors optimizing facemask performance.

It is now unequivocal that differences exist between different VHCs, which in a number of cases are sufficiently large that meaningful and overt clinical differences would be anticipated as a result. However, until recently there had been a lack of clinical studies of adequate scale and design which explored such issues. This perhaps explains why, despite a large volume of (principally *in vitro*) literature, few clinical and regulatory guidelines explicitly advocate that VHCs are not interchangeable. The concordance between *in vitro* and *in vivo* outcomes evident in more recent clinical studies may start to change that paradigm.

With specific regards to the AC+FV aVHC, it builds on a substantial literature base that exists for earlier AeroChamber variants. That literature base includes clinical data for virtually all innovator pMDIs currently approved in the US and EU, supporting the safety and efficacy of those pMDIs, in conjunction with the AC+ VHC. The consistency of respirable dose delivery through the charge dissipative AC+FV aVHC for different active

substances, with immediate delivery and prolonged delay, in coordinated and uncoordinated simulations has been demonstrated. These data suggest overt advantages for the AC+FV aVHC *versus* non-conducting VHCs, but also illustrate performance differences alongside other antistatic VHCs. Comparative data for the AC+FV aVHC/ComfortSeal facemask combination *versus* other VHC/facemasks support the attainment of a tight seal with the application of a relatively low force, which are a function of its design and constituent materials, allied to a low deadspace which renders it appropriate for infants. A combination of the above features is likely to be implicated in the results of a recent real-world database study that demonstrated the benefits of the AC+FV aVHC over non-conducting spacers in a predominantly paediatric/adolescent population. Such studies may represent a viable and cost-effective research paradigm to probe for clinical differences between VHCs in future evaluations.

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Conflict of interest statement

Dr Suggett is an employee of Trudell Medical International, the manufacturer of the AeroChamber VHC family. Dr Dissanayake is a consultant at Certior Consulting Ltd and was engaged by Trudell for this project.

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